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CHAPTER 5

Male Genital System

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GENERAL CONSIDERATIONS

The pathology of the male reproductive system is closely linked to theriogenology, so the clinical significance and pathogenesis of lesions and diseases are very important. For each species, there is a short list of common diseases. We highlight these for each anatomic location.

Information on basic mechanisms of reproductive disease in companion animals is gleaned and extrapolated from a variety of human, laboratory animal, and/or toxicologic studies. There are physiologic differences between species that can impact outcome, however. Diseases of production animals are frequently handled pragmatically by culling and replacement, so in-depth studies are not always available.

The bridge between theriogenology and pathology is hindered by differing meanings of diseases. *Orchitis* is a common clinical diagnosis to denote any swelling of the scrotum, rather than its literal "inflammation of the testis." Similarly, the ability of spermatozoa to stimulate a florid inflammatory reaction is overlooked, and epididymal "abscess" is used even though there may be no or few neutrophils. *We highlight those terms where the clinical meaning differs from the usage in pathology.*

From a functional and pathogenetic point of view, the male reproductive system is designed to deliver viable spermatozoa to the female. It is composed of a production unit (the testis), a maturation and maintenance unit (epididymis), and a transportation unit (various parts of the ducts and accessory genital glands). Each will be dealt with in turn. The male still comprises 50% of the reproductive unit.

Sampling of the male genital tract

The foundation of macroscopic and histologic evaluation of any system is the *problem-based approach*. The standard diagnostic protocol is to interpret clinical information, develop diagnostic hypotheses or differential diagnoses, and perform suitable tests to confirm or exclude the possible causes. Each test, such as macroscopic evaluation, will exclude some possibilities and perhaps add others. Eventually a final diagnosis can be reached. Evaluation of each component of the male genital tract requires knowledge of normal anatomy. For a thorough examination, all components should be examined carefully. Examination of the accessory genital glands usually requires their removal from the pelvis.

For histologic evaluation of the majority of components of the male tract, standard collection procedures apply and formalin fixation and paraffin embedding is adequate and cost effective. The testis, however, requires a separate approach. Although the function of the testis is the same for each species, this organ varies greatly both in its anatomy, histology, and response to injury. It is important to know the resistance

of the testis of each species to autolysis and handling pressure. It is also important to know the orientation of the testicular mediastinum, efferent ductules, and the seminiferous tubules. The type and number of samples collected will also depend on the suspected diseases.

One of the simplest evaluations is for testicular neoplasia. Standard formalin-fixed paraffin-embedded samples of testicular tumors are sufficient for diagnosis. Evaluation of the stages of spermatogenesis requires much more sophistication.

The first step in evaluating spermatogenesis is to determine how sensitive the testis is to handling pressure and autolysis. It is best to fix testicular tissues within minutes of anesthesia or euthanasia and removal. The testes of rams, for example, require immediate fixation, whereas bovine testes can remain refrigerated for several hours. The testes of some species are susceptible to the effects of handling and the pressure applied while tissue slices are made. It is best to always use sharp instruments and to minimize pressure on the testicular parenchyma during sampling.

Fixation of the testis will depend on the end use. Formalin fixation is adequate for cursory evaluation of spermatogenesis for all species. Detailed evaluation requires the tissue to be fixed more rapidly and or rendered harder to withstand histologic section production. Bouin's solution is a mainstay for many laboratories. It is readily available. Davidson's fluid is now being used by many laboratories. Embedding in plastics or acrylics is superior to paraffin but is much more expensive and requires specialized equipment and training.

Testicular diseases affect different parts of the testis and different parts of each seminiferous tubule. The number and location of sections depends on the unique characteristics of the species at hand and the types of suspected diseases. Macroscopic evaluation of the testis usually directs location and size of appropriate histologic samples. For example, rams often develop degeneration dorsally and bulls ventrally. Small ruminants often develop initial degenerative lesions of the seminiferous tubules near the testicular mediastinum.

The evaluation of testicular histology will also vary with the orientation of the seminiferous tubules. In general, the seminiferous tubules are oriented perpendicular to the testicular mediastinum. A sample taken from the mediastinum to the testicular capsule will provide multiple cross sections of a small number of seminiferous tubules. A sample taken parallel to the mediastinum will sample a limited portion of many more seminiferous tubules. Routine sampling requires sagittal sectioning of the testis, multiple transverse sections (bread-loafing), and fixation of testicular tissue so that histology can be examined from an appropriate region of normal and abnormal testis both along and across the path of the seminiferous tubules.

Spermatogenesis

Spermatogenesis is a complex process involving stem cells, gene expression, cellular interactions, apoptosis, and cytokine and other hormonal interactions. It is clear that testicular function in general, and spermatogenesis in particular, requires a complex interaction of all cells within the testis and not just germ cells, Sertoli cells, and interstitial endocrine (Leydig) cells.

The testis is divided into the tubular and extratubular compartments. The cells within the tubules are the Sertoli cells and the germinal cells—spermatogonia, spermatocytes, spermatids, and spermatozoa.

Sertoli cells are very complex in their structure and function. The majority of Sertoli cells are present at birth or soon after. They extend from the basement membrane to the lumen, and have a large surface area. Attachment between adjacent Sertoli cells and to germinal cells is by a variety of junctional complexes, and this forms a major part of the blood-testis barrier. Sertoli cells function to maintain the integrity of the germinal cells, compartmentalize the germinal cells into basal and luminal compartments, secrete fluid, form the tubular lumen, phagocytose degenerating and dead cells, deliver nutrients to germinal cells, metabolize steroids, translocate germinal cells, secrete proteins, regulate the spermatogenic cycle, and mediate hormonal effects on the germinal cells. These many functions are potential targets for abnormalities.

Spermatogenesis begins with stem cells that proliferate by mitosis, undergo a meiotic phase, and finally differentiate. These stages correspond to *spermatogonia*, *spermatocytes, and spermatids*, respectively. The spermatogonia are divided into proliferative and differentiating types of stem cells. They divide by mitosis to produce the cells that go on to form spermatozoa. Meiotic division has a prolonged prophase, but subsequent phases proceed rapidly. The spermatids are formed as a final, differentiating step. *Spermiation* is the active release of spermatozoa by Sertoli cells to the lumen, for subsequent transport through the duct system.

Spermatogonia are exposed to testicular interstitial tissue fluids. Occluding junctions of Sertoli cells mostly form the *blood-testis barrier*. Spermatocytes and spermatids within the tubule are "external" to the blood-testis barrier. Apoptosis of germ cells at each stage of development occurs as a natural phenomenon (see later), and Sertoli cells take up degenerative and dead cells.

Control of spermatogenesis involves a complex interaction of central endocrine and local paracrine-autocrine factors. Central factors involve the hypothalamic-pituitary-gonadal axis. Gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. Interstitial endocrine cells have LH receptors that, when coupled with LH, produce testosterone. Testosterone is essential for spermatogenesis and several other testicular functions; Sertoli cells, germinal cells, and myoid cells have androgen receptors, but the contribution of testosterone for the function of germinal cells and myoid cells is not known. Testosterone is known to inhibit apoptosis of germ cells. FSH directly stimulates the Sertoli cells and perhaps the germinal cells. FSH and testosterone probably act synergistically. FSH action on Sertoli cells results in release of the hormones estrogen, inhibin, and activin. Estrogen is important in the function of other cells and spermatogenesis. Inhibin and activin are members of the transforming growth factor (TGF) superfamily. Inhibin enters the blood stream and inhibits FSH production, whereas activin stimulates FSH production. Both also have local effects and are part of the paracrine-autocrine system. Sertoli cells also produce *anti-Müllerian hormone* (AMH, previously known as Müllerian inhibitory substance [MIS]) during development but usually not in adults.

Local control of spermatogenesis is also highly dependent on local paracrine and autocrine factors; the number of factors recognized is increasing exponentially. The extensive crosstalk

between all cell types is essential for spermatogenesis and for controlling inflammation and the altered immunocompetent state of the testis. Germinal cells, Sertoli cells, peritubular myoid cells, and interstitial endocrine cells secrete many cytokines and growth factors. These cells are influenced, in turn, by a large number of similar signaling molecules. Also important in spermatogenesis is the presence of death receptors on germ cells, in particular, Fas (APO-1, CD95), a transmembrane receptor molecule that transmits an apoptotic signal in the cell when it is bound by a Fas ligand. Sertoli cells express Fas ligand, and regulators of apoptosis are found in the testis, including the Bcl-2 family of proteins and the p53 protein. Apoptosis is a normal phenomenon regulating cell populations, but induction of apoptosis or increased apoptosis also occurs with exposure to toxic compounds, depletion of growth factors, alteration of hormonal support, exposure to heat or radiation, transient ischemia, free radical status, or treatment with drugs. Testes with impaired spermatogenesis, such as hypospermatogenesis or maturation arrest, may have increased apoptosis. There are also antiapoptotic proteins and substances produced in the testis that counterbalance apoptotic pathways.

There are well-recognized changes in spermatogenesis with **age**. There is a dramatic increase in testicular size at the time of puberty. The seminiferous tubules increase in length and diameter, and the testicular volume increases. The size of the testis then decreases progressively from puberty into adult life. From early adulthood onward, there is a gradual reduction in tubular diameter. The absolute number of Sertoli cells probably declines from puberty on. A decline in the number of spermatocytes and an increase in apoptosis both contribute to reduced testicular mass to various degrees in different species. A concurrent increase in the mass of the testicular interstitial tissue typically occurs with age, and the basal lamina of the seminiferous tubule increases in thickness.

Domestic mammals usually have continuous spermatogenesis from puberty until death; however, there is species variation in the percentage of seminiferous tubules with active spermatogenesis. Spermatogenesis is normally divided into stages, and a single cross-section of a seminiferous tubule has a single stage. An adjoining length of the same seminiferous tubule will have a different stage, but not necessarily the next stage. A complete series of stages over time becomes the cycle of the seminiferous epithelium. Not all seminiferous tubules have complete stages of spermatogenesis at any one time, and every species has what is termed normal background change that mimics changes seen at puberty or resulting from a degenerative event. This is particularly the case in boars.

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Oxidative stress and testicular function

Antioxidative systems are important factors in normal testicular and epididymal function and, by extension, diseases of the testis. The high rates of cell division cause high rates of oxygen consumption in a low oxygen tension environment. This is combined with large amounts of unsaturated fatty acids and the presence of systems to generate reactive oxygen species such as xanthine and NADPH-oxidases and cytochrome P450. The intratubular compartment is particularly vulnerable to oxidative stress and free radical damage.

The protective systems include antioxidant enzymes and free radical scavengers, such as intracellular superoxide dismutase, glutathione peroxidase, and glutathione-S-transferase. The balance between production and removal is of major importance in spermatogenesis.

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Testicular immune function

Testicular parenchyma is a unique immunologic environment. Both innate and acquired immune function is actively suppressed. This environment is maintained by testosterone and its influence on peritubular myoid cells, endothelial cells of capillaries, veins and lymphatic vessels, and testicular macrophages. This environment is maintained partially because spermatocytes, spermatids, and spermatozoa are antigenic, and outside the blood-testis barrier. *Any condition that causes leakage of spermatozoa or spermatozoal antigens into the extratubular compartment is potentially complicated by inflammatory and immunologic responses*. The response to spermatozoa is variable, but innate or nonspecific immunity and acquired mechanisms including humoral and cellular defences are involved. This also occurs in the tubules and ducts of the reproductive tract, including the epididymis.

Spermatozoa incite a foreign body/granulomatous response, and degradation is slow because of their number and composition of fatty acids, lipids, phospholipids, and keratin molecules.

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In addition, immune responses are florid and many plasma cells and CD4 and CD8 lymphocytes are present. Up-regulation of major histocompatibility complex (MHC) II in epithelial cells also occurs. The reaction leads to chronic inflammation and fibrosis, and continued obstruction and disruption of tubules. Spermiostasis, spermatocele, and/or further sperm granulomas are the consequence.

Antispermatozoal antibodies are found in serum, genital secretions, or both. They occur in infertile individuals in several species, including humans. There is a lack of information on their presence in genital fluids, where they have the greatest impact. Spermatozoal antigens gain entry to the interstitium as a result of trauma, rupture of a duct or tubule, or leakage from either failure of the barrier between tissue and spermatozoa following inflammation or obstruction. Specific conditions include blind-ended efferent ductules (spermatic granuloma of the epididymal head or efferent ductules), segmental aplasia of the mesonephric ducts, adenomyosis, and epididymitis. Infection of dogs with *Brucella canis* can cause the formation of antispermatozoal antibody, and it occurs in vasectomy and other causes of obstruction of ducts.

Serum immunoglobulin may gain access to the spermatozoa through any part of the reproductive tract, but the efferent ductules and epididymis are probably the most accessible sites, because the barrier between the internal and external compartments is less tight. Local immunoglobulin production can occur at any location in the tract, but the accessory genital glands are the most common site (see later).

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Immunity in the reproductive tract

Innate and acquired immunity occur in the male genital tract. Both male and female reproductive tracts have a unique ability to co-opt immune cells for normal physiologic functions. There are different populations of cells of a similar type—some that are involved in regulation of spermatogenesis and others that are proinflammatory. Testicular macrophages/antigen-presenting cells are present in the normal interstitial tissues of all species and their importance is increasingly recognized. They are involved in the regulation of spermatogenesis, steroidogenesis, and immune regulation. Those that reside in the testis contribute to reduced immune function to form a tolerant environment maintained by natural killer (NK) and regulatory T (Treg) cells. Lymphocytes entering the testis are proinflammatory but must overcome the local environment. Systemic inflammatory disease affects testicular function by the stimulation of immune and inflammatory pathways. Pattern recognition receptors such as toll-like receptors are important in this.

The male genital tract has little ability to compensate for direct injury. The testes are bound by the tough and relatively inelastic capsule, and any sudden increase in internal pressure or swelling, be it caused by hemorrhage or edema, results in testicular necrosis. Injury to the seminiferous tubules can result in a breakdown of the blood-testis barrier and subsequent immune reactions. The epididymis and deferent duct form a single small-diameter tube that is easily obstructed and damaged, and it is free from the usual systemic immune surveillance. There is always the specter of inflammation and acquired immunity to spermatozoal or secretory products.

Normally, little immunoglobulin enters the seminal fluids, and with a few exceptions, lymphocytes are rare in the interstitium of reproductive structures in normal male animals. Those entering the testis are actively destroyed.

Epithelium throughout the reproductive ducts and ductules can express MHC II molecules if inflammation is present. The various ducts of the male reproductive tract contain intraepithelial leukocytes, especially CD8 lymphocytes. The accessory genital glands are believed to be the main location for plasma cells, which presumably add immunoglobulins to the seminal fluid to help prevent access of ascending agents to the deferent duct and epididymis. Local humoral immunity develops in the accessory genital glands, and is predominantly IgA-based in several species.

One of the unfortunate side effects of having spermatozoa not recognized as "self" is the necessity of maintaining these cells completely separate from immune surveillance. This provides microbial organisms a location within the lumen of ducts and tubules where they can grow and cause damage. Once the body recognizes the injury and recruits inflammatory cells, there often is too much damage to permit repair or regeneration. In addition, the very processes of inflammation, including the release of free radicals by leukocytes, damage the tract further. As in many other sensitive tissues, *the damage done by inflammation may be a major cause of dysfunction.*

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DISORDERS OF SEXUAL DEVELOPMENT

Disorders of sexual development (DSD) include all congenital anomalies of the reproductive tract including those of a major or minor nature.

Production of a normal ejaculate depends on the normal development of the reproductive tract, including normal spermatogenesis, spermatozoa maturation and transport, normal accessory genital gland function, and nervous, musculoskeletal, and psychological factors.

Sexual differentiation requires appropriate sequential gene expression; production of proteins and other hormones; receptor expression; and the complex development and regression of the paramesonephric (Müllerian) ducts, mesonephric

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(Wolffian) tubules and ducts, and the tissues of the gonadal ridge/primitive bipotent gonads. When all steps occur normally, sex chromosome genotypic, gonadal, and phenotypic sex is matched. Male domesticated mammals normally have an XY genotype, although XX males can occur if a sex-determining factor is present.

SF1 is a gene activated at the beginning of the sex determination period in both males and females, but it reduces in amount dramatically at the end of the sex determination period in males. It is also involved in the development of adrenal and hypothalamic-pituitary axis. In normal XY males, *SRY*, the gene that is the sex-determining region of the Y chromosome, encodes a transcription factor that contains a high mobility group (HMG)-box DNA binding domain. This binds to specific DNA sequences, causes bending of the DNA and results in Sertoli cell differentiation. *WT1+KTS*, *GATA4* and *FOG2* are part of the transcriptional or post-transcriptional regulation of *SRY*. SRY, the product of *SRY*, regulates transcription by binding to promoter sites of *SRY*-like HMG-box protein 9 (*SOX9)*. *SOX9* also has 2 transcriptional activation domains that act on the testis determining pathway. *M33* (Cbx2) and *ATRX* are involved in gonadal development. SRY, M33, and ATRX either activate testis-determining genes or inhibit pro-ovarian genes.

SRY is very important in Sertoli cell development, and testes do not develop unless there are sufficient Sertoli cells. Formation of Sertoli cells is influenced by many genes and products, including *SF1* and *AMH*, the gene that produces anti-Müllerian hormone (AMH). Activation of *AMH*, which causes regression of the paramesonephric ducts, marks the end of the sex determination period in males. *DAX1* is a gene that appears to act downstream of *SRY* and is important in early Sertoli cell differentiation. DAX1 inhibits the male sex determining pathway, and if *DAX1* is activated in males, a female develops.

As part of testicular development, endothelial cells migrate from the mesonephros to the testis. The formation of this extra vasculature is important in testis development, especially sex cord formation. At this time, the formation and function of the interstitial endocrine (Leydig) cells is acquired. Thus the formation of the Sertoli cells, interstitial endocrine cells and vasculature combined is necessary for testis development. Interstitial endocrine cells develop from the same cell population as the adrenal cortex, that is, from vascular smooth muscle cells and pericytes of testicular capillaries—vascular cell types that act as stem cells. *SF1*, desert hedgehog gene (*DHH*), and *PDGFA* are involved with this. Also *ARX* (the homeobox gene aristaless-related) has a function.

During early embryonic development, primordial germ cells (PGC) migrate to the gonads and there are many genes and gene products that can be detected. They are not necessary for testicular development. Testicular cord development results in the blocking of PGC proliferation in the G0/G1 phase of mitosis and they differentiate into prospermatogonia.

The constituents of the primitive gonad are the germ cells, mesenchymal cells, coelomic epithelial cells, and mesonephric epithelial cells. These form the 4 major cell types in the gonad—the germ cells, supporting cells, steroid-producing cells, and unspecialized mesenchyme. SRY causes the germ cells to go into mitotic arrest, the supporting cells become the Sertoli cells, the steroid-producing cells become the interstitial endocrine cells (of Leydig), and the mesenchyme develops the testicular pattern. The mesonephric tubules form the rete testis and the efferent ductules. The epididymis, deferent ducts, and vesicular glands are derived from the mesonephric ducts. The prostate and bulbourethral glands form from the urogenital sinus, and the penis, prepuce, and scrotal sac develop from the urogenital sinus and tubercle when testosterone is present.

The male phenotype depends on the production by the Sertoli cells of AMH, which causes the paramesonephric (Müllerian) duct to regress. Interstitial endocrine cells produce testosterone and INSL3 that inhibits further female differentiation, prevents the mesonephric ducts from regressing, and induces development of the prostate, bulbourethral glands, penis, and scrotum.

The testis, epididymis, and associated structures descend from the urogenital ridge into the scrotum. Testicular and epididymal descent occurs in 3 main stages: *the relative transabdominal migration phase, the intra-inguinal phase, and extra-inguinal migration*. Testosterone is not necessary for testicular descent but it does assist in the growth of the vaginal process and gubernaculum. The first phase may be partially controlled by AMH, the second phase requires increased intra-abdominal pressure, and the third involves interaction of androgen, calcitonin gene-related protein, the genitofemoral nerve, and perhaps other factors. In early fetal life, a cranial gonadal suspensory ligament supports the testis. It may be retained when there is a lack of androgens, in which case subsequent development of the *testicular gubernaculum* also is impaired. The testicular gubernaculum is a gelatinous cord of tissue that extends from the caudal pole of the testis to the inguinal area and it exerts traction on the testis. A mutation in the *GREAT* gene, which is highly expressed in the gubernaculum and may mediate response to hormones, has been associated with intra-abdominal cryptorchidism in humans and, experimentally, in mice. The exact mechanisms are yet to be elucidated in domestic mammals, but they no doubt are complex and involve an interrelationship of systemic and local factors.

The effects of endocrine disruptors on male development are increasingly important, because multiple disorders of sexual development, such as reduced anal-genital distance, delayed preputial separation, hypospadias, and ectopic and maldescended testes, can all be induced by antiandrogenic and estrogenic chemicals (the endocrine disruptors).

Disorders of sexual development (DSD) are now divided into 3 general categories: sex chromosome DSD, disorders with an XX genotype (XX DSD), and XY DSD. XX and XY DSDs are divided into groups based on whether the gonads are normal or not. Many DSD result in a female or feminine phenotype and are considered in more detail in Vol. 3, Female genital system. Those mentioned here are mostly DSD with a male genotype, gonads, or genitalia.

- *Sex chromosome DSD* are those with an altered sex chromosome complement such as the classic XXY (Klinefelter syndrome). These are manifested clinically as ambiguity in phenotype and/or infertility. Animals with **XXY chromosomes** or a mosaicism with XXY chromosomes may have hypoplastic internal genitalia. Well known of these are male *tortoiseshell or calico cats*. They are almost always infertile, and have testicular hypoplasia. Hybrids of the horse and donkey (with 64 and 62 chromosomes, respectively), the mule and hinny, have 63 chromosomes and are sterile. The classic sex chromosome DSD in animals is the freemartin (Fig. 5-1).

Figure 5-1 A bovid with a sex chromosome disorder of sexual differentiation (**freemartinism**). There is gonadal dysgenesis, the tubular genitalia are predominantly mesonephric (male) including vesicular glands, and there are female external genitalia with a prominent clitoris.

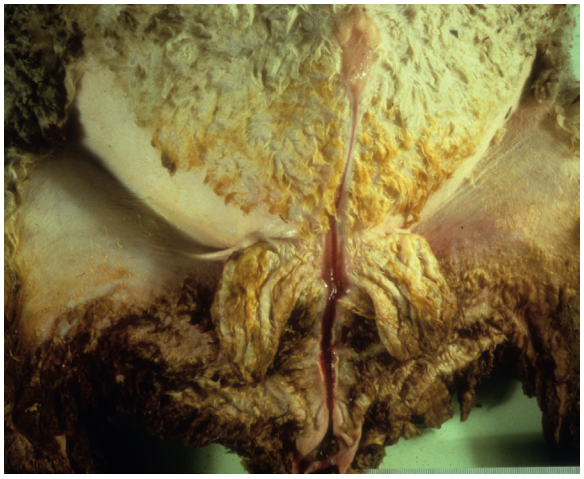

Figure 5-2 A ram lamb with **complete hypospadias**, including bifurcation of the scrotum.

- *XX DSD* with abnormal gonads have a female genotype but have either testes or ovotestes. They have varying development of male and female internal genitalia. They are usually masculinized and some may be indistinguishable from normal males. Such cases, commonly called *XX sex reversal*, are reported in most species. In goats this is called the *polled/intersex syndrome* (PIS) because it is common in polled animals, in which polled XX homozygotes have both male and female gonads (true hermaphrodites); loss of the *FOXL2* gene product is responsible. They range from sterile males to females with testes. Dogs of the American Cocker Spaniel breed are commonly affected. In pigs, it is a common DSD confused with freemartinism.
- *XY DSD* form the largest group because any disorder of development of the male genital tract in genotypic males is included. Common DSD such as *hypospadias* (Fig. 5-2), *cryptorchidism* (Fig. 5-3), *testicular hypoplasia* (Fig. 5.4), and *cystic remnants of embryonic ducts* (Fig. 5-5) are all now categorized in this group.
- The most extreme type of XY DSD are those animals with a *normal female phenotype but with an XY genotype and gonads that are testes* (their full category name is XY, *SRY*+,

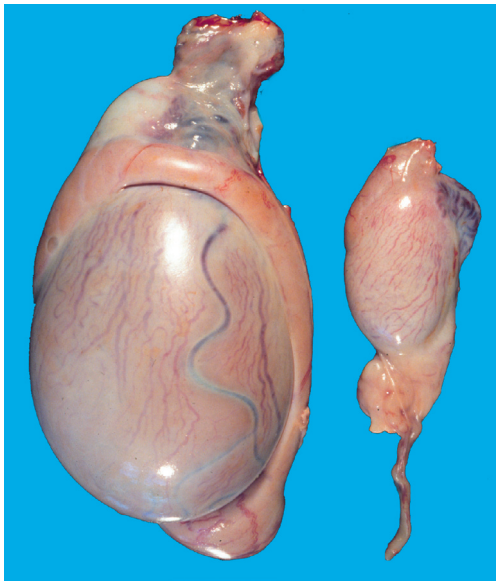

Figure 5-3 Unilateral **abdominally retained testis** (right) from a ram. The contralateral testis (left) was within the scrotum and is more bulbous than normal because of compensatory hypertrophy.

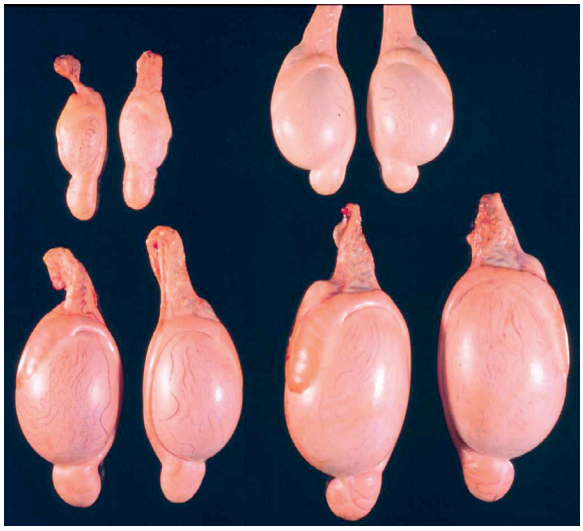

Figure 5-4 Testes and epididymides of 4 rams of the same age. There is a gradation of **testicular hypoplasia** from severe (upper left) to normal (lower right).

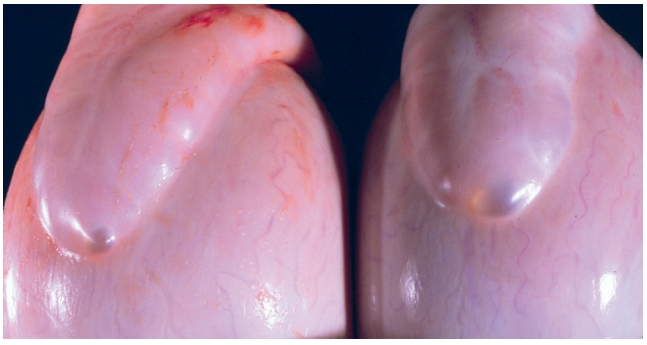

Figure 5-5 Bilateral congenital **retention cysts** at the junction of the head of the epididymis and testis of a ram.

Figure 5-6 Miniature Schnauzer dog with an **XY disorder of sexual development** commonly called **persistent Müllerian duct syndrome**. This dog was phenotypically male with retained testes (sectioned) and well-developed uterine horns and body.

testicular DSD, with female phenotype). These usually lack androgen receptors—they have testes, no tubular genitalia, but are phenotypically female. All species develop this type of DSD.

- A well-recognized but less extreme form is found in Miniature Schnauzer dogs that are XY, *SRY* +, testicular DSD with male phenotype and retention of paramesonephric ducts (Fig. 5-6). They lack functional anti-Müllerian hormone (AMH) receptors and have a syndrome called *persistent Müllerian duct syndrome* (PMDS). Affected Miniature Schnauzer dogs may develop hydrometra and pyometra. Many are also cryptorchids.

Gynecomastia is occasionally seen as a solitary lesion in males. There are reports of bucks from high milk production lines that develop mammary glands. It also occurs in hyperestrogenism syndromes.

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SCROTUM

The scrotum is an outpouching of perineal skin with an inner lining of peritoneum and direct communication with the peritoneal cavity. Many terrestrial mammals have their testes within a scrotum, but the reason is the subject of theories. In these species the intrascrotal temperature is less than core temperature. Most assume the testis must be lower in temperature but the epididymis also may operate better when cooler. The maturation of spermatozoa is a slow process and the epididymis is one long and coiled tube. The testicular artery is long and coiled, and changes the blood flow from pulsatile and high pressure to a constant low-pressure system. This makes the oxygen tension in the testis lower than expected, and the oxidant-antioxidant balance is less robust. The blood supply to the epididymis is separate and shorter.

The scrotum maintains the testis and epididymis at a temperature less than core. The scrotal skin is thinner than skin elsewhere and has little or no subcutaneous fat or connective tissue. It is lightly haired, except in the cat, and has prominent apocrine sweat glands. The contractility of the scrotum is a property of the *dartos tunic* that consists of fibroelastic tissue and smooth muscle. Thermoregulatory function is shared with the *cremaster muscle*, which regulates the proximity of the testis to the abdominal wall, and the *pampiniform plexus* of testicular artery and veins, which ensures maximum contact of cooled venous blood with the warmer arterial blood. If the testes of the common domestic animals are at or above normal body temperature, degeneration of the seminiferous epithelium occurs. Retained testes do not develop normal spermatogenesis or testicular and epididymal size.

The formation of the scrotum from the paired genital swellings of the embryo, and its full development at puberty, requires testosterone and is dependent on the development of normal testes. *Disorders of scrotal development* include absence of the scrotum in cryptorchidism. A bifurcated scrotum and scrotal clefts or notches represent failures of fusion of the paired primordia. These may be isolated defects, accompanied by hypospadias (see Fig. 5-2) and other defects such as atresia ani, or occur in a variety of disorders of sexual development.

Enlargement of the scrotum can be the result of lesions of the scrotal skin, vaginal tunics and cavity, testis, epididymis, pampiniform plexus, inguinal canal, and superficial inguinal lymph node. Disease of each of these anatomic regions is covered later in this chapter.

Thickening of the scrotal skin and dartos tunic is mostly due to edema of local or systemic origin, or because of inflammation or neoplasia. The skin of the scrotum can be part of disease of the skin elsewhere. We will concentrate here on diseases that primarily affect the scrotum.

In **bulls**, scrotal dermatitis is caused by contact with irritant substances from the environment, ectoparasites such as biting insects (*Simuliidae* and *Culicoides*), lice (*Haematopinus eurysternus*), and mites (*Chorioptes bovis*); fungi; protozoa (*Besnoitia besnoiti*, *Trypanosoma* spp); bacteria (*Dermatophilus*

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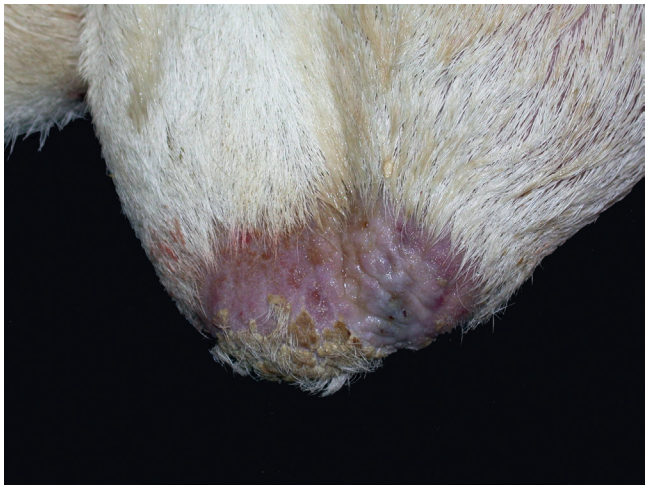

Figure 5-7 **Scrotal frostbite** in a ram.

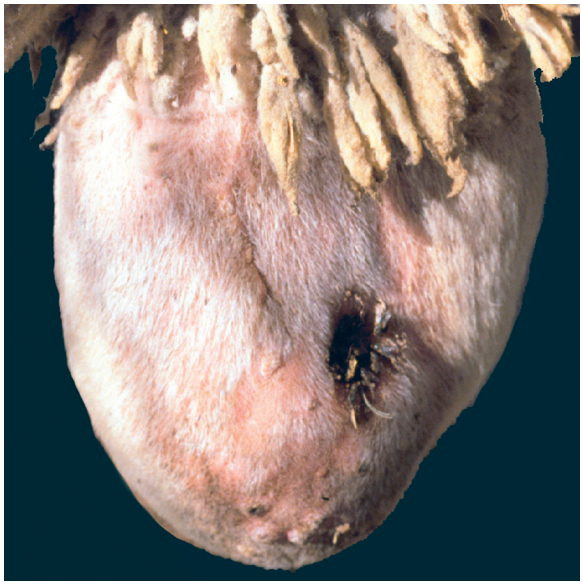

Figure 5-8 **Fistulous tract** through the scrotum of a ram with severe epididymitis and periorchitis.

congolensis); and viruses (poxviruses) to name a few. These may occur as diffuse or focal lesions.

Range bulls and occasionally rams exposed to extreme cold may develop *scrotal frostbite* (Fig. 5-7). A higher incidence of lesions in old bulls is attributed to their more pendulous scrotums. Lesions are well demarcated regions of necrosis of skin on the ventral aspect of the scrotum and can involve up to 75% of the scrotum. Scrotal swelling, tunic adhesions, and decreased semen quality accompany the more severe lesions. The scrotal skin of bulls is especially susceptible to infection by *Dermatophilus congolensis*. Severe, prolonged infection may result in thickening of the skin to 1 cm, with advanced testicular degeneration and infertility. Infection of scrotal skin by *Besnoitia besnoiti* also may lead to severe testicular degeneration. This infection is not limited to skin, and the small nodules containing white gritty material are seen grossly in the subcutis of the scrotum as well as in the tunics, the parenchyma of the testis, and in the epididymis. Vascular damage is important in the development of lesions, and large numbers of *Besnoitia* cysts may be present in the intima of vessels in the pampiniform plexus. Neoplasia is rare in bulls, but papilloma, melanoma, and hemangioma occur. *Varicose dilations of scrotal veins* occur in older bulls. They appear as flattened and irregular thickenings of the scrotal skin. The overlying epithelium usually is normal unless it ulcerates and bleeds. The affected venous channels are irregular in shape, widely dilated, and have thickened walls; thrombosis occurs in many.

In **boars**, hemangiomas are common. They are multiple exophytic and variegated or papillary lesions that may bleed. They do not appear to affect fertility. Such lesions are benign and may not be true neoplasms. Age, altered hemodynamic forces in the capillary bed of the scrotal dermis, and genetic predisposition are factors that might be involved in their development. Any cutaneous disease of the pig could potentially affect the scrotum.

In the **stallion**, trauma from the kick of a mare occurs and the local effects include swelling and edema plus ulceration and hemorrhage. Abscessation can occur. The scrotum is often affected in dependent edema from systemic and or intestinal diseases as an extension from preputial edema. Peritonitis, equine viral arteritis, and other vasculitides including purpura hemorrhagica, and surra, caused by *Trypanosoma evansi* infection, are potential causes. Dourine (*Trypanosoma equiperdum*) affects the prepuce and can secondarily affect the scrotum. Parasitic dermatitis occurs in horses—mostly from the secondary effects of self-trauma from rubbing. Biting flies, including *Culicoides*, and *Onchocerca* microfilariae in the scrotal skin can lead to dermatitis. Eosinophilic superficial perivascular or nodular dermatitis will occur; microfilariae will be found in onchocerciasis. *Habronema* larvae infect wounds of the scrotum and cause large granulomatous nodules. The most common neoplasm of the skin of the horse is the equine sarcoid, and scrotal masses may occur. Melanoma of the perineum involves the scrotum rarely.

In **rams**, parasitic dermatitis from *Chorioptes bovis* is common and the scrotum appears to be a preferred site for the mite. The lesions can be mild but are frequently sufficiently severe to cause testicular atrophy and infertility. In such cases there is marked thickening of skin and matting of overlying hair and wool by secretions and exudate. *Linognathus pedalis*, the foot louse of sheep, can also affect the scrotal skin. Cutaneous myiasis and dermatophilosis rarely affects the scrotum. Draining tracts through the scrotal skin from periorchitis and epididymitis may occasionally occur (Fig. 5-8).

In **bucks**, sarcoptic mange, with typical crusted lesions and thickening of the skin, can involve the scrotum.

In **dogs**, disease of the scrotum is uncommon. Pyoderma, both superficial and deep, and folliculitis and furunculosis can affect the scrotum. *Brucella canis* is reported to cause scrotal dermatitis and ulcers, but many cases are the result of licking and self-trauma from the pain and discomfort of epididymitis and periorchitis. *Ehrlichia* spp and *Rickettsia rickettsii* may cause scrotal edema, infarction, and ulceration from vasculitis. Fungal infections of the scrotum occur in dermatophytosis and infection with *Microsporum* and *Trichophyton spp. Mallassezia* and other yeasts such as *Candida* species can affect the scrotum too, and they produce a superficial intraepidermal pustular and hyperplastic disease. Blastomycosis (*Blastomyces dermatitidis*), sporothricosis (*Sporothrix schenckii*), and prototheocosis (*Prototheca wickerhamii*) cause nodular pyogranulomatous dermatitis. Protozoal infections of the scrotum include leishmaniasis (*Leishmania* spp) and have the typical lesions of

a plasma cell–rich or pyogranulomatous nodular-to-diffuse dermatitis. Parasitic diseases of the scrotum of dogs include infection with *Cuterebra emasculator*, which results in a draining tract from an abscess and local necrosis of the tissue. *Sarcoptes scabiei*, *Demodex* species, and *Pelodera strongyloides* affect the scrotum, as they do in other locations. Migration of hookworm larvae can also occur through scrotal skin. Of the many other cutaneous diseases seen in dogs, contact irritant and hypersensitivity reactions occur, as does atopy, food hypersensitivity, fixed drug eruptions, and a plethora of immune-mediated diseases. The scrotum can be affected by physicochemical injury including burns, sunburn, abrasions and lacerations from fighting and motor vehicle accidents, and frostbite. Neoplasms of the scrotum include any neoplasm of skin, and if they are common elsewhere in skin, they are likely to occur on the scrotum. Examples include mast cell tumors and vascular tumors such as hemangiomas and hemangiosarcoma. There does not appear to be any increased susceptibility to a particular neoplasm in this area.

In both **cats** and **camelids**, bite wounds from other males occur in the scrotum. Other primary spontaneous scrotal disease is rare.

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VAGINAL TUNICS

The vaginal tunic is a membrane of dense fibrous tissue overlaid with a single mesothelial layer continuous with and structurally similar to the peritoneum. The scrotum and intrascrotal contents are covered by the parietal and visceral layers, which form the boundaries of the cavity of the vaginal tunic.

The cavity of the vaginal tunics communicates with the peritoneal cavity and is susceptible to the accumulation of ascitic fluid. Fluid within the cavity around the scrotal contents is called **hydrocele**. It forms for exactly the same reasons as ascites. Hydrocele may lead to severe testicular degeneration on the involved side and to a lesser extent on the opposite side. Scrotal hydrocele, with diminished sperm quality, is a herd problem in bulls in some regions. Clinically, the fluctuant nature of the enlarged scrotum, with a scrotal circumference up to 60 cm, is indicative of edema, and if affected bulls are examined at autopsy, there is obvious ascites. If hydrocele persists, the tunics become increasingly fibrotic. Ostertagiasis and hemotropic mycoplasma (*Mycoplasma wenyonii*) infection are incriminated as causes of this syndrome. Hydrocele in other species occurs with ascites of heart failure or any other cause of fluid buildup in the peritoneal cavity. It can also occur in conditions that cause edema of the scrotum (as listed previously).

Hematocele is the accumulation of blood in the vaginal cavity. It is the result of trauma and is seen in stallions with mating injury and in boars housed together.

The visceral tunic is an integral part of the testicular capsule. It is composed of inelastic collagen and fibrous tissue, and smooth muscle through which the vascular tunic is normally visible. In spite of the presence of smooth muscle, the capsule is not significantly contractile; it probably contributes to the flow of semen by maintaining intratesticular pressure. The tunic is thickened and opaque in testicular hypoplasia and atrophy.

Inflammatory changes in the vaginal tunic may be part of disseminated infection, with typical lesions of feline infectious peritonitis, tuberculosis, caseous lymphadenitis, and diseases causing polyserositis in all species. Suppurative and fibrinous inflammation also occurs as an extension of scrotal injury or from epididymitis. Inflammation of the tunics is often called *periorchitis*.

Severe periorchitis is a complication of epididymitis irrespective of cause, but is particularly found in bulls with *Trypanosoma brucei* infection, in rams infected with *Brucella ovis* or *Actinobacillus seminis* (Fig. 5-9), and dogs with *Escherichia coli* epididymitis (Fig. 5-10). *Setaria labiatopapillosa* causes granulomatous periorchitis in bulls, and lesions occur particularly after adults are killed by anthelmintic treatment. A high prevalence of eosinophilic, then granulomatous, periorchitis in water buffaloes is attributed to *Setaria* sp. Ectopic parasites, such as migrating equine strongyle larvae (*Strongylus edentatus*), can be found on the tunics. Periorchitis in rams is very common in infectious epididymitis. *Pyocele* or hemipyocele is reported rarely as a spontaneous condition and is reported in the ram with *Staphylococcus capitis* infection. Cysts of taenid larvae, mostly *Cysticercus tenuicollis*, may be found in the scrotal cavity of rams, without inflammation. In dogs, rare

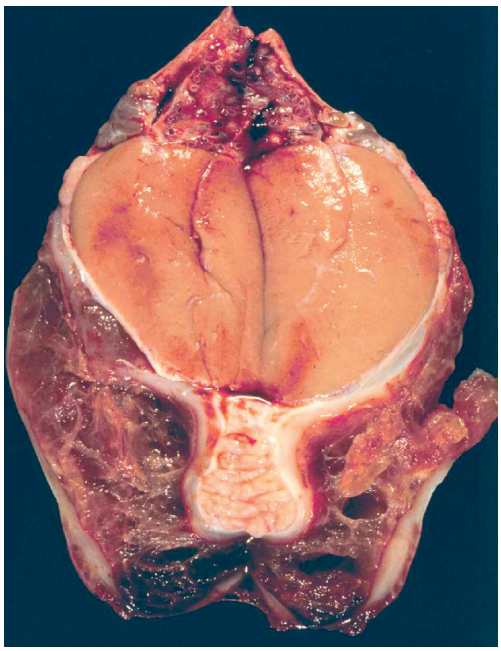

Figure 5-9 **Periorchitis** secondary to epididymitis in a ram. Fibrin and edema fluid are present within the cavity of the vaginal tunics.

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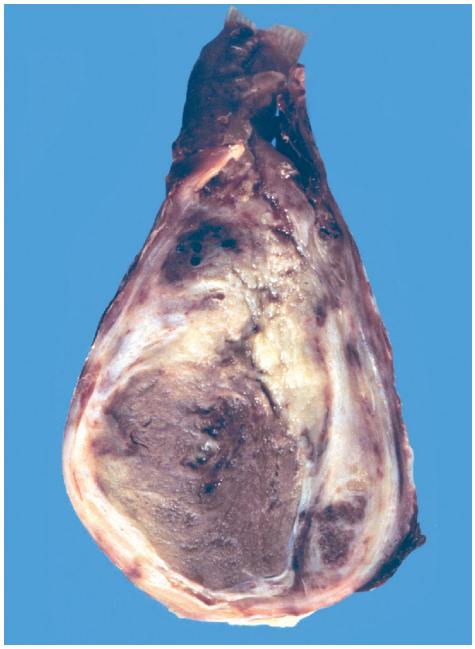

Figure 5-10 Severe epididymitis and periorchitis in a dog. The tail of the epididymis is large and edematous, and there is fibrin and exudate in the cavity of the vaginal tunic. The testis is necrotic. The ventral scrotum was ulcerated from self-trauma.

peritoneal cestodiasis caused by larvae of *Mesocestoides* spp. may involve the vaginal tunics, with saccular dilations within the tunics, thickening of the spermatic cord, and pyogranulomatous inflammation involving the testicular capsule and extending into the testes. There is also a report of pentastome larvae of *Porocephalus crotali* within the testicular capsule of a dog.

Adhesions between the visceral and parietal layers of the vaginal tunic are common, especially in older animals. Adhesions are at first fibrinous, reflecting acute periorchitis (see Fig. 5-9), but later become fibrous. Fine, thread-like, fibrous adhesions located at the epididymal tail in bulls are normal. Extensive adhesions result from infectious periorchitis secondary to epididymitis. Most adhesions are focal and solitary, and do not have lesions in the testis or epididymis; they probably are of little consequence.

Cystic lesions of the vaginal tunic may be loculations within adhesions. Very small cysts, probably of paramesonephric duct origin, are common adjacent to the head of the epididymis in the horse, and are referred to as *appendix testis* or Morgagni's hydatid. In rams they are called *inclusion cysts* (see Fig 5-5).

Neoplastic disease *involving the vaginal tunic is rare*, even as secondary extension from the testis or scrotum. *Mesotheliomas* with primary involvement of the vaginal tunic occur in the dog and bull (Fig. 5-11). Extension of the tumor into the peritoneal cavity has been observed in the dog. Ultrastructural study or immunohistochemistry is necessary to differentiate mesotheliomas from metastatic adenocarcinoma. The origin of intrascrotal mesothelioma from the paramesonephric duct remnant is suggested. There is a report of a lipoma occupying the right scrotal cavity in a ram, causing compression of, but apparently not directly involving, the testis.

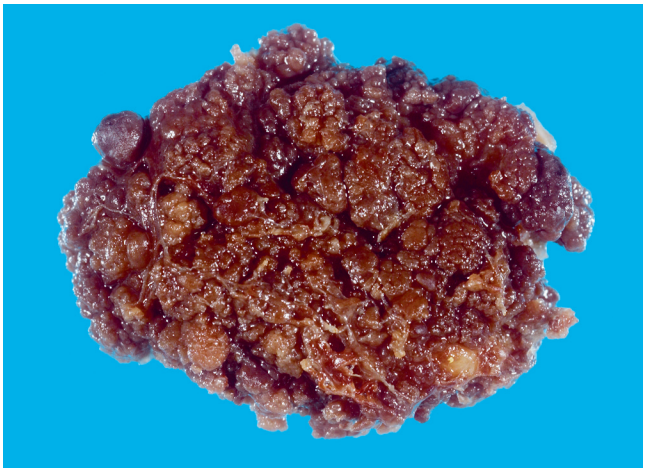

Figure 5-11 Papillary **mesothelioma** of the vaginal tunic that completely covers the scrotal contents of a dog.

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TESTIS AND EPIDIDYMIS

Spermatozoa develop in the *seminiferous tubules* and pass through the *straight tubules* into the *intratesticular rete* within the mediastinum testis. They leave the testis via the *rete testis* and enter the *efferent ductules*. The efferent ductules number between 13 and 20, depending on the species. Most join the single duct of the *epididymis*, but it is common in most species for one or more to end blindly. The epididymis is long and tortuous, and divided into many distinct areas. For this discussion, 3 main areas will be referred to: the *head, body, and tail*. The tail terminates in the *deferent duct*. Disease of one area has effects on other regions.

Pathologists often examine the testes or biopsies of individual animals rather than whole groups of animals. Gross and histologic assessment of reproductive tissues is a valuable tool if used appropriately. Complete definition of a clinical problem often requires collaboration of the cytogeneticist, endocrinologist, theriogenologist, and pathologist, who alone may not be able to determine the complete pathogenesis. For the pathologist to function optimally, appropriate samples must be collected and processed. For many of the diseases and the tissues, routine fixation with 10% formalin is adequate, but for

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a detailed assessment of spermatogenesis, or the histologic appearance of seminiferous tubules, rapid fixation after death or collection (within minutes in many species) in Bouin's, Zenker's, or Davidson's fluid, with paraffin embedding, is necessary. Plastic embedding is the method of choice for a detailed assessment of the spermatogenic cycle. Inadequate fixation or suboptimal processing of testicular tissues will cause artifacts that cannot be distinguished from degeneration.

The normal testis is pale pink or even almost white. This is presumably because of the large quantity of chromatin material. Abnormalities that result in a lowering of spermatogenesis result in the dominance of other pigments—especially lipochrome pigment. The testes of boars become progressively brown with age, and are brown if degenerate. *A frequent misdiagnosis is made in equine fetal and neonatal gonads.* Fetal testes undergo hypertrophy because of hyperplasia of the interstitial endocrine cells as they produce precursors for placental hormones. These cells and testicular macrophages contain lipochrome pigments that are especially noticeable during the atrophic stage that occurs prior to birth. Many a practitioner and pathologist are fooled by the apparent brown discoloration of the testicular parenchyma of the neonatal equine testis (Fig. 5-12). The testis varies in gross and microscopic appearance among the species. The stallion has prominent fibrous tissue septa; it is less prominent in the dog and boar, and absent in ruminants.

Sampling of the testis should be planned. Taking a random sample of any part of the testis is adequate for generalized disease; however, such a sample may not be representative of the entire testicular parenchyma. There is species and individual variability in the part of the testis initially affected by degenerative processes, including variations between the dorsal and ventral parts of the ruminant testis, variations between seminiferous tubules, and along the length of individual seminiferous tubules. *Sampling of the testis to maximize the number of seminiferous tubules examined should be at right angles to the direction of the tubules.* In general, the seminiferous tubules run at right angles to the mediastinum. Each forms a loop that begins and ends at the mediastinum, and turns completely at the testicular capsule. In ruminants, the testes are oriented in a dorsoventral plane, the stallion has a more craniocaudal orientation, the dog is oblique, and the boar and cat are inverted oblique. The basic microscopic appearance is similar—the testis is divided into the *interstitial (extratubular) or intertubular compartment* and the *seminiferous tubular compartment*. The interstitial endocrine cells are the major resident of the intertubular compartment; macrophages are another important cell type. In the boar, the interstitial endocrine cells are particularly prominent and numerous (Fig. 5-13). In young horses, there are lipofuscin-containing macrophages in the interstitium, remnants of gonadal atrophy of the fetal gonad (Fig. 5-14). The normal tubular diameter is 270 µm in the bull, 146 µm in the stallion, 180 µm in the dog, and 236 µm in the boar. It is normal to see spermatogenic arrest in some seminiferous tubules in some species.

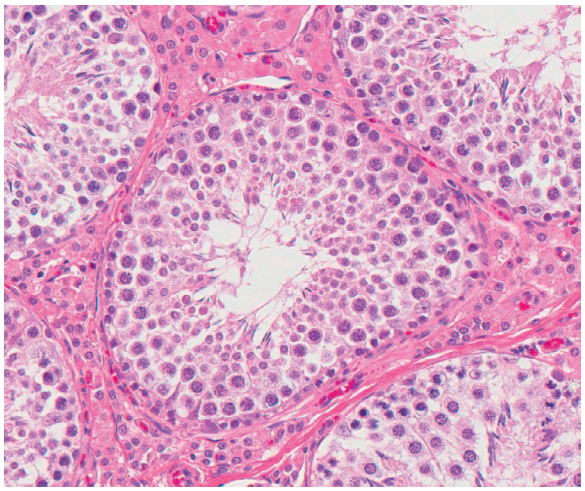

Figure 5-13 Normal spermatogenesis within a **normal seminiferous tubule** of an adult boar. Note the prominent interstitial endocrine cells.

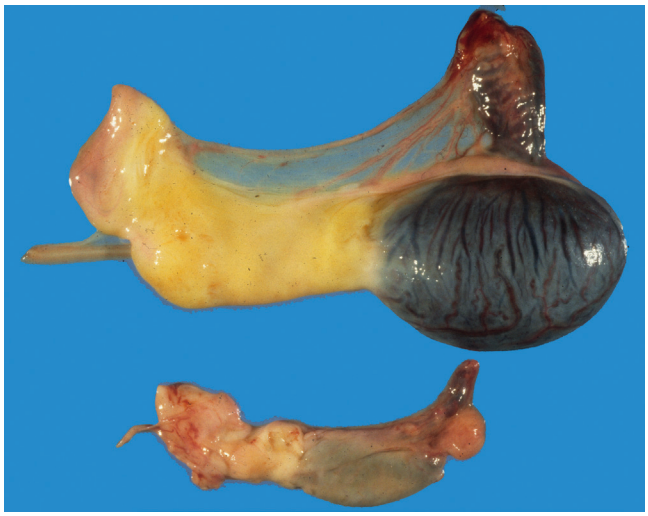

Figure 5-12 Equine fetal testis and epididymis (upper) with **physiologic gonadal hypertrophy**; testis is dark brown. Testes undergo atrophy to become the size of the **normal neonatal testis** (lower) before passing through the inguinal ring.

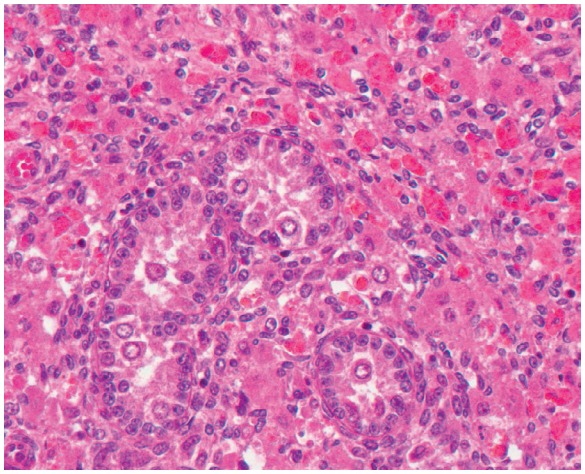

Figure 5-14 **Testis of a neonatal foal** with prominent interstitial cells, macrophages containing lipochrome pigment, and immature seminiferous tubules that have prominent and centrally located germ cells.

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Disorders of sexual development

Nomenclature and classification of anomalies of the reproductive tract has changed and all are now called disorders of sexual development (DSD, see previous section). Also listed earlier are the normal processes involved in development of each component of the reproductive tract. Factors that apply to individual species are listed later.

Cryptorchidism

Incomplete descent of the testes and associated structures (cryptorchidism) is one of the most common DSD of the male reproductive system. Its classification is XY, *SRY*+, testicular DSD with failure of testicular descent. It is the most common genital abnormality of the stallion and tomcat. Descent of the testes, epididymides, and spermatic cord (including the testicular artery and vein and the deferent duct) is a complex series of events. Individual cases may be due to chromosomal, hormonal, structural, or environmental causes. Complete testicular descent usually occurs before birth in most species, with the exception of the dog.

Maldescent creates several problems. Most cases are presumed to be inherited, and breeding from affected individuals is not recommended. *Retained testes lack spermatogenesis*, and fertility is compromised. Increased rates of testicular neoplasia occur with cryptorchidism in several species, most notably the dog. Finally, *testicular torsion* is found almost exclusively in maldescended testes, although the stallion is an exception.

Diagnostic pathologists receive tissue removed during cryptorchidectomy to confirm it is testis. The retained testis fails to develop after puberty and resembles an immature testis. Over time, it degenerates or undergoes torsion and only a small remnant remains (Fig. 5-15). The most difficult cases are those in which all that remains is dense fibrous tissue and lipofuscin-containing macrophages. *Anorchia* is very rare and, where possible, differentiated from degeneration or death of a retained testis.

A *hereditary basis* for cryptorchidism is established or suggested in all species. In addition, chromosomal abnormalities are present in some rams, bulls, and stallions. Multiple studies of human males with cryptorchidism show that 2-4% have sex chromosome disorders of the sex chromosomes; thus this is a manifestation of a chromosomal DSD. When there are outbreaks of cryptorchidism, hormonal and environmental factors are more likely. Failure of descent sometimes occurs because structural disorders anchor the testis so it cannot migrate to the scrotum. Splenogonadal fusion, retention of the cranial gonadal suspensory ligament, and abnormalities of the gubernaculum and vaginal process are all reported.

Retained testes in prepubescent animals are identical to descended testes prior to puberty. Germ cells are in the lumen of the tubules or close to the basement membrane in their normal location. In postpubertal animals, the testes are smaller than their normal scrotal counterparts (see Fig 5-3) and often have a "Sertoli cell only" pattern (Figs. 5-16, 5-17). This is because of the deleterious effect of normal body temperature on spermatogenesis. In older animals, degenerative changes such as interstitial fibrosis and thickening of basement membranes are superimposed on the immature appearance. In extreme forms, the outlines of distorted basement membranes are in fibrous tissue (see Fig. 5-15). Hyperplastic foci of Sertoli cells occur in some retained testes, and these may be sites of development of Sertoli cell tumors (see Fig. 5-17). In unilateral testicular maldescent, which is typical, the contralateral testis is hypertrophied (see Fig. 5-3).

Cryptorchidism is infrequently reported in **bulls,** but the prevalence is much higher. Retention of the testis and epididymis is mostly in the subcutaneous/inguinal region, and occurs about twice as often on the left as compared to the right side. Polled Hereford and Shorthorn cattle are more at risk than other breeds. Little is known of the pathogenesis of cryptorchidism in bulls, although it is believed to be hereditary. The histologic appearance of the cryptorchid testis is similar to

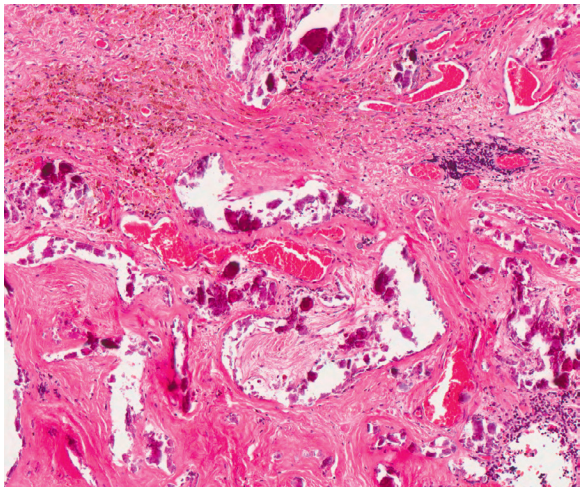

Figure 5-15 End-stage retained testicular tissue with marked interstitial fibrosis, mineralized remnants of seminiferous tubules, and lipofuscin-containing macrophages.

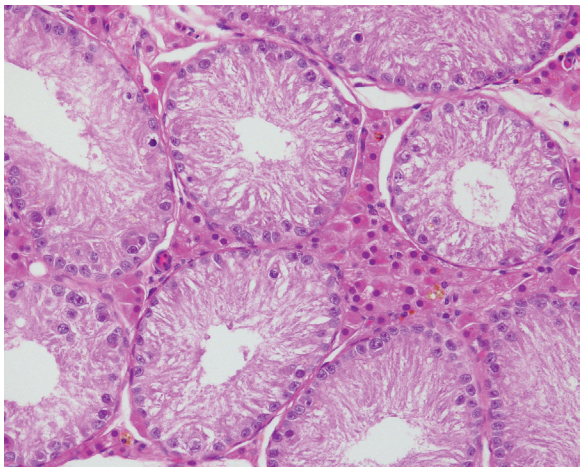

Figure 5-16 Testicular hypoplasia in a boar, with arrested spermatogenesis. Appearance is identical to immature testis.

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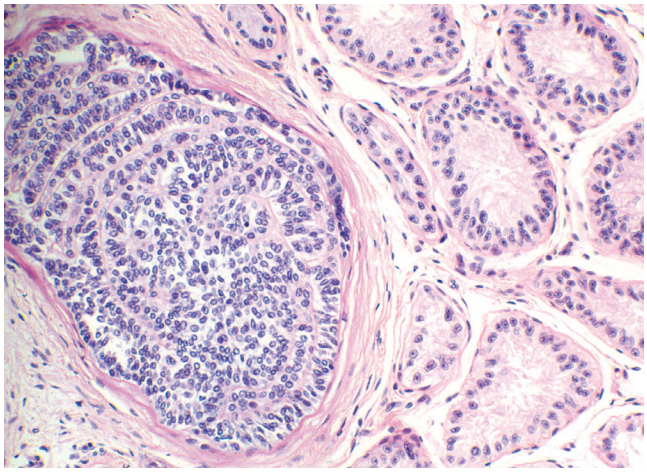

Figure 5-17 Focal **Sertoli cell hyperplasia** in the cryptorchid testis of a ram.

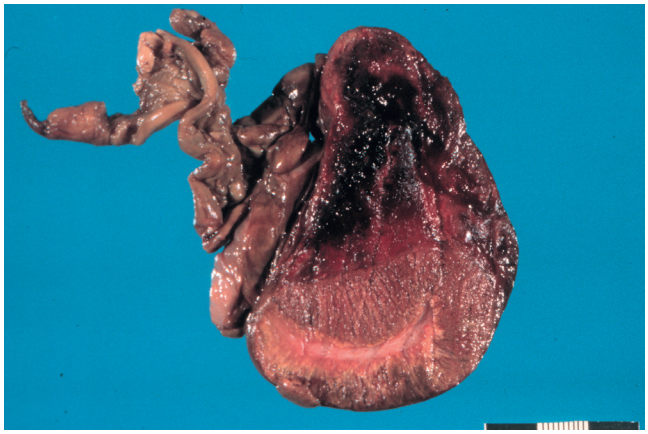

Figure 5-18 **Torsion** of the retained testis of a boar.

that of hypoplastic testes and epididymides. Neoplasia in cryptorchid testes is very rare in bulls, with an interstitial cell tumor and a fibrolipoma reported.

Cryptorchidism is common in **boars**. There is a hereditary basis, with the trait being recessive, and there may be recessive genes at more than one locus in the Duroc breed. Abnormal development of the gubernaculum, including underdevelopment, excessive growth, and an abnormal location, is the main underlying structural change in cryptorchidism in pigs. The usual location for the retained testes in pigs is intra-abdominal, and torsion is seen in slaughtered pigs (Fig. 5-18).

There are many reports of cryptorchidism in **stallions.** Testicular retention is usually unilateral, with about equal frequency as to side affected. Abdominal retention of left testes is more common than inguinal; the reverse is the case on the right side. Neoplasia of the retained testis is occasional, with teratomas, seminomas, and Sertoli cell tumors reported.

In **rams**, cryptorchidism often has an autosomal recessive mode of inheritance, but may also be due to a dominant gene with incomplete penetrance. Unilateral maldescent is more common (see Fig. 5-3) than bilateral involvement, and the right testis is most often retained. Hemicastration is likely in unilateral cryptorchid animals. Some ram lambs, inadvertently, have only their scrotum removed during attempted castration, leaving the testes in an "induced cryptorchid" state.

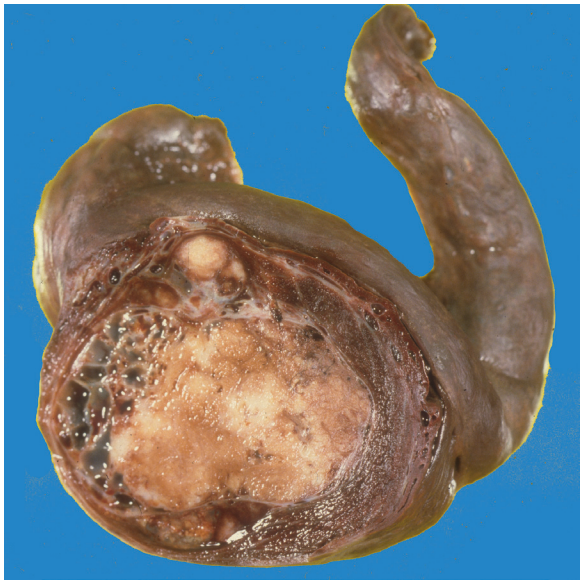

Figure 5-19 **Intra-abdominal testis** of a dog that developed a Sertoli cell tumor. The testis subsequently underwent torsion and venous infarction.

Cryptorchidism in sheep has an increased prevalence in polled animals.

Cryptorchidism occurs sporadically in **goats,** mainly involving the right testis. It is a regular feature of the goat disorder of sexual development known as the polled/intersex syndrome (PIS).

In **dogs**, cryptorchidism may be an autosomal recessive inherited disease in some breeds, although there is some doubt that this is the main cause. Although it is a frequent clinical finding, little is known of the mechanism and features of the condition. The association between testicular neoplasia and testicular maldescent is well recognized. Sertoli cell tumors are the most common, especially in abdominally retained testes. Seminomas are the second most common neoplasm, and they occur mostly in inguinally retained testes. Miniature Schnauzers with persistent Müllerian duct syndrome (PMDS) often have unilateral or bilateral testicular maldescent. Testicular torsion usually involves cryptorchid testes—especially if there is a concomitant testicular neoplasm (Fig. 5-19). Other diseases linked to retained testes are patellar subluxation, hip dysplasia, penile and preputial defects, and umbilical and inguinal hernias. Dogs are more likely to have retention of the right testis—perhaps because of a longer pathway for descent of that testis, or a less well-defined gubernaculum on the right. Inguinal testes predominate over intra-abdominal. Testicular neoplasms—Sertoli cell tumor and seminoma—are more prevalent in the right side also. Descent is usually complete by 3 months of age in the dog. Hormonal studies suggest that LH is lower in cryptorchid dogs, and the cryptorchid testis mediates the inhibition of LH secretion. As with other species, cryptorchidism could indicate a sex chromosome DSD (see previous section, Disorders of sexual development).

Cryptorchidism is the most common disease of the reproductive tract in male **cats,** and Persians are over-represented. The failure of testicular descent in cats tends to be unilateral without a bias to one side or the other. The testis can be anywhere along the migration path, although inguinal cryptorchidism predominated in one study.

Camelids can have retained testes, with a prevalence of about 3% in alpacas. The testes are often inguinally retained.

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Testicular hypoplasia

Hypoplastic testes fail to grow to a normal size. *Testicular hypoplasia occurs in sex chromosome DSD, cryptorchidism, and as an "uncomplicated" disease*. This latter situation is categorized as an XY *SRY*+ testicular DSD. It can be unilateral or bilateral, and is confirmed after puberty when an immature testis does not develop to its expected normal size. The small size is because of a reduction in the amount of seminiferous epithelium, thus there are fewer Sertoli cells, spermatogonia, spermatocytes, elongated spermatids, and spermatozoa. An affected testis is grossly similar to a normal prepubertal testis in almost every way (see Fig. 5-4).

Studies of hypoplasia are mostly observational at the clinical, gross, or microscopic level. Evaluation of mutant mice has aided the study of pathogenesis, mostly by identifying the effects of lack of cytokines and growth factors. Research indicates there is an alteration of control of spermatogenesis, so there are many similarities with testicular degeneration (see later). From a pathogenetic point of view, hypoplasia occurs when spermatogenesis is affected prior to or at the time of puberty, and degeneration occurs from a similar cause after puberty.

Hypoplasia is known or suspected to be hereditary in the bull, ram, and buck. The exact genetic abnormality is often not established. There are few studies of hypoplasia in domesticated animals, but there are some special features of the disease in selected species discussed later.

Hypoplasia is the potential outcome of a large number of different abnormalities that may operate at a systemic or local level. The small size of the testis is theoretically because of an abnormally small number, length, or diameter of tubules, or one or more combinations of these (see Figs. 5-14, 5-16, 5-17). Germ cells may be absent, or be present but fail to produce enough spermatozoa. Thus germ cells may fail to migrate to the genital ridge in utero, fail to migrate in sufficient numbers, fail to survive, have arrested development, undergo excessive apoptosis, or undergo degeneration (Fig. 5-20). The underlying cause can be abnormal sex chromosomes (thus a sex chromosome DSD), a deficiency of gonadotropins, or other altered environment of the testis during development.

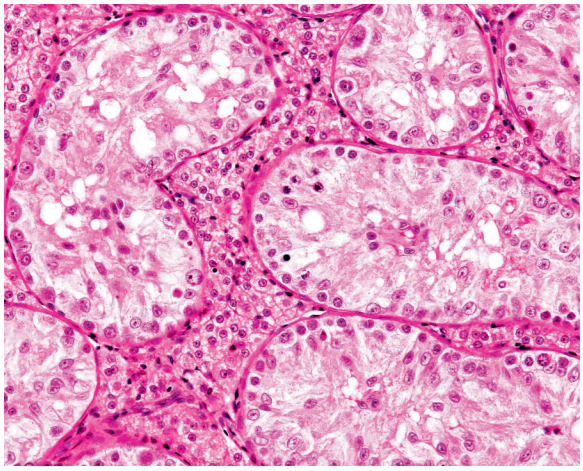

Figure 5-20 Testicular hypoplasia in a cat. Seminiferous tubules contain only Sertoli cells and a few germ cells. There is some degeneration of Sertoli cells with vacuolation. The interstitial endocrine cells are very prominent.

At the sex chromosome level, testicular hypoplasia is recognized in animals with a condition resembling Klinefelter syndrome. Affected, bulls, pigs, horses, sheep, dogs, and cats have an XXY genotype or a mosaicism with XXY chromosomes. The best known of these is the male tortoiseshell or calico cat. In Saanen goats with the gene for polledness (PIS), testicular hypoplasia is seen in individuals that have XX sex chromosomes but have testes and a male phenotype. A variety of other sex chromosome abnormalities are identified with hypoplasia.

A deficiency of gonadotrophins occurs with hypoplasia (hypogonadotrophic hypogonadism) in men and mice, but studies in domesticated mammals indicate a normal or raised serum concentration of FSH and LH. Testosterone concentration was lower than normal in some bulls with hypoplasia; in sheep, testosterone and inhibin concentration may be normal.

Microscopic abnormalities include a total lack of germ cells, arrested spermatogenesis in all tubules, or arrested spermatogenesis that varies from tubule to tubule (see Fig. 5-20). Hypoplastic testes with a total lack of germ cells are very small and fail to enlarge from their size at birth (see Fig. 5-4). Those testes with arrested development of all tubules fail to progress beyond a certain stage of spermatogenesis. It is common to see some hypoplastic tubules in a normal testis.

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Hypoplasia in bulls. Testicular hypoplasia in bulls, and especially in some breeds such as the Belgian blue, is very common. Breeding soundness examination and the culling of bulls with a scrotal circumference below the normal range is common and in some breeds exceeds 90% of tested individuals. The causes are probably multifactorial. Studies suggest it is hereditary in the Swedish Highland breed, in which it has a recessive inheritance with incomplete penetrance. Animals with white body and ears are particularly likely to have hypoplasia. The majority of unilateral hypoplastic testes are on the left side. In one *Bos indicus* breed, heritable hypoplasia is linked to branching of the testicular artery near the aorta of the same side, suggesting that reduced blood flow may be responsible. Testosterone secretion was reduced in the affected testis.

Microscopic changes of hypoplasia include cessation of spermatogenesis at some stage, with either degeneration or excessive apoptosis of the germinal epithelium. The most severe cases of hypoplasia have a Sertoli cell-only pattern or they have some normal and abnormal tubules intermixed, often with affected tubules being in the more dorsal part of the testis.

Persistent infection of bulls with bovine viral diarrhea virus (BVDV) may affect testicular development.

Hypoplasia in boars. Most research on boar fertility and altered spermatogenesis has focused on chromosomal abnormalities, including abnormal complement of sex chromosomes, translocations of parts of the X chromosome, and other disorders. These result in abnormal spermatogenesis or inability to produce an appropriate litter size in the face of normal semen parameters. Porcine reproductive and respiratory syndrome virus (PRRSV) infection of the testis and increased apoptosis of germ cells is reported and may contribute to infertility of infected boars.

Hypoplasia in stallions. Testicular hypoplasia of horses is not well studied and prevalence is not available, partly because most male horses are gelded. It occurs with sex chromosome DSD and as a sporadic condition. Many cases are mild and unilateral—one testis is smaller than the other.

Hypoplasia in rams. Testicular hypoplasia of rams is consistently the most commonly reported DSD of the male reproductive tract. It is usually a sporadic disease that is either bilateral or unilateral. The disease is not well studied. A condition resembling Klinefelter syndrome, with an XXY genotype, is reported. Zinc deficiency is implicated in some cases.

Various degrees of hypoplasia are recognized, and affected testes may have tubules that, at the extreme are ~90 μm in diameter (normal 160 μm) and lined by mostly fetal Sertoli cells. There is a report of an outbreak of gonadal hypoplasia of multiple rams born within a short time frame. The affected testes were uniformly small and had a "Sertoli cell-only" pattern histologically. An environmental cause was suspected.

Hypoplasia in bucks. There are several types of hypoplasia recorded in bucks. It is a common abnormality in the polled/intersex (PIS) syndrome of polled Saanen goats, in which the animals have XX sex chromosomes but have testes and are phenotypically male. The testes of affected animals have rudimentary seminiferous tubules. Other sporadic forms of hypoplasia occur, and the cause is not known.

Hypoplasia in cats. Testicular hypoplasia is a sporadic disease of cats. In male cats with a tricolor or calico coloration and therefore a XXY sex chromosome complement, there are no germ cells and the testes are markedly hypoplastic with small diameter tubules. Chimeric animals may be fertile.

Hypoplasia in dogs. About 6% of dogs may have testicular hypoplasia. A diagnosis is usually made after azoospermia is found during an investigation of infertility. Congenital azoospermia occurs in some lines of dogs. This suggests a familial or hereditary basis, implicating inbreeding. Confirmation of congenital azoospermia because of testicular hypoplasia requires historical information or testicular biopsy after the expected date of puberty.

Hypoplasia occurs in animals with failure of testicular descent and in sex chromosome abnormalities such as those with XX or XXY sex chromosome DSD. Offspring of bitches treated with diethylstilbestrol may have hypoplastic testes.

Other testicular disorders of development

Monorchia is the presence of only one testis. As a general term, *monorchism* is the result of cryptorchidism, severe unilateral testicular degeneration, or agenesis. *True agenesis* occurs when there is a failure of one testis to develop. The differentiation between true agenesis and a cryptorchid with total testicular degeneration is impossible, but true agenesis is considered to be very rare. Likewise, *supernumerary testes* (polyorchidism) or *fusion of abdominal testes* is very rare.

The presence of testicular tissue outside the testis is reported in pigs, in which nodules of tissue were found throughout the peritoneal cavity. In the dog and cat, Sertoli cell tumors and interstitial cell tumors can arise from ectopic testicular tissue in the scrotal skin or spermatic cord. Previous surgical implantation of normal cells is suspected. In the cat, heterotopic interstitial endocrine cells occur in the epididymis, and neoplasia of this tissue is reported.

Fusion of the testes to abdominal organs such as the spleen and variations in the shape of testes are described. "Hour-glass" shaped, round, and horizontally placed testes of ruminants are all reported.

Accessory or ectopic adrenal tissue is reported in horses and rams, and rarely in other species. Most are located in the region of the head of the epididymis and distal spermatic cord (Fig. 5-21).

A variety of cystic structures have been described in and around the testis and epididymis. Some arise from the rete testis and others are remnants of mesonephric ducts or ductules, or paramesonephric ducts.

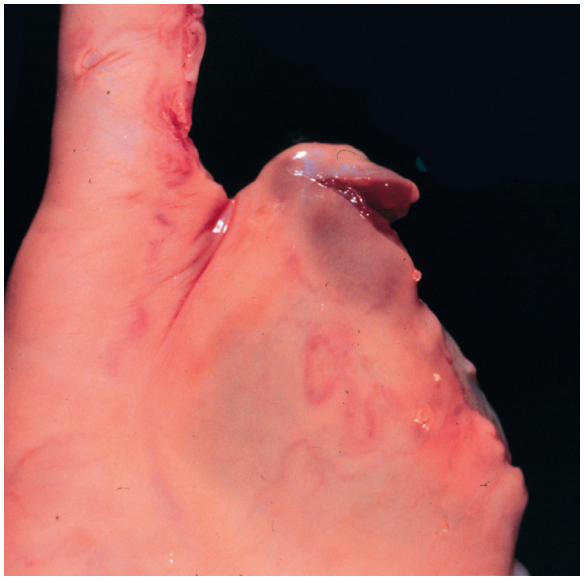

Figure 5-21 Ectopic adrenal nodule (cut) on the deferent ductule region of a ram.

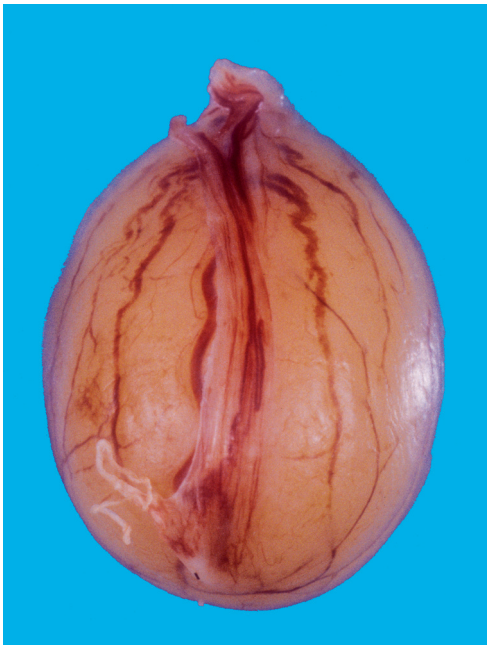

Figure 5-22 Segmental aplasia of the mesonephric duct in a cat. The entire epididymis is missing. The deferent duct remains on the bulbous testis

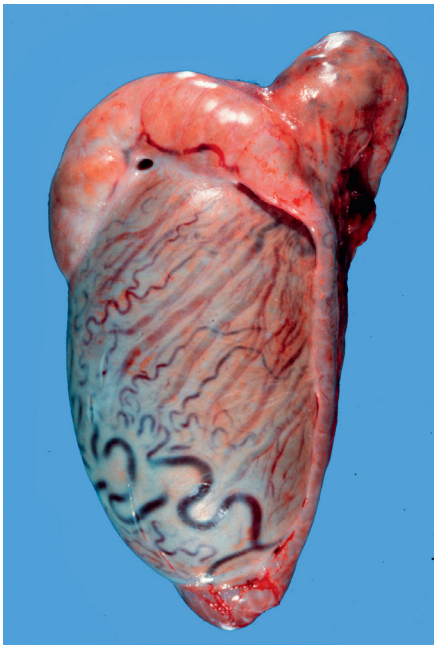

Figure 5-23 Spermatic granuloma of the epididymal head in a bull. The efferent ductular region and the head of the epididymis are large and contain spermatic granulomas. The body and tail of the epididymis is very small.

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Disorders of mesonephric and paramesonephric structures

The rete testis and efferent ductules are derived from the mesonephric tubules. The epididymis, deferent duct, and ampullae (and vesicular glands) form from the mesonephric duct. These transport spermatozoa and fluid from the testis to the pelvic urethra. Maturation and storage of spermatozoa also occurs in this conduction system. There is a single duct from the efferent ductules to the urethra, and any interruption has catastrophic effects to the fertility of that side. The eventual effect of continuous spermatozoal production and disruption of one of the efferent ductules has a similar outcome.

Segmental aplasia of the mesonephric duct (SAMD) is an important condition because it prevents fertility of the affected side. Segmental aplasia is rare, but found in all species. Unilateral aplasia may be an inherited condition. Absence of the tail of the epididymis is the most frequently recognized DSD (Fig. 5-22). Without a part of the epididymis, continuous production of spermatozoa results in spermiostasis, tubular dilation, formation of spermatic granulomas, dilation of the mediastinum testis, and testicular atrophy from increased pressure. A smaller vesicular gland on the affected side—presumably because of a lack of trophic stimuli—is usually also present. Hypertrophy of the contralateral testis is likely.

Spermatic granuloma of the epididymal head (Figs. 5-23, 5-24) results from failure of one or more of the 12-25 efferent ductules to join with the epididymal duct. After puberty, the blind-ended ductule(s) fill with spermatozoa and, with spermiostasis, may rupture and/or form a spermatic granuloma. The induced inflammation and fibrosis will eventually cause obstruction of other efferent ductules and the epididymal duct. The result will be complete obstruction to flow of spermatozoal-rich fluid and progressive formation of more spermatic granulomas. The distal epididymal tissues do not reach adult size, the mediastinum testis dilates, and the testis undergoes pressure atrophy. This condition is misdiagnosed as infectious epididymitis and the potential congenital

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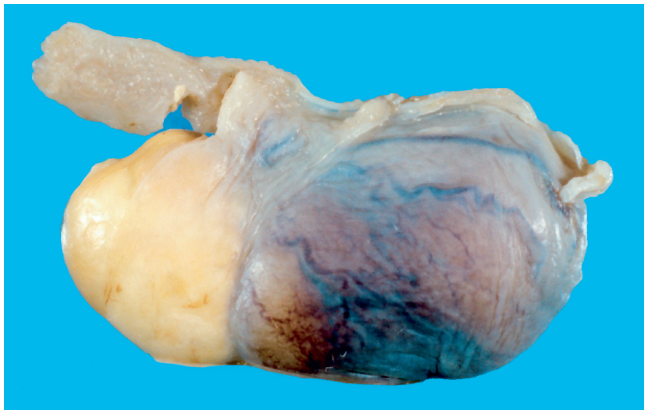

Figure 5-24 Spermatic granuloma of the epididymal head in a dog.

or hereditary basis for the problem is missed. Spermatic granuloma of the epididymal head is a more commonly found in polled Saanen goats, where they may be bilateral, and in Boston terrier dogs (see Fig. 5-24).

Many *cystic lesions* are reported in the testicular capsule, epididymis, spermatic cord, and adjacent to the accessory genital glands. These are dilated remnants or duplications of the mesonephric tubules or paramesonephric and mesonephric ducts. Their location in the reproductive tract is the best indicator of their origin. Remnants of the mesonephric duct include the paradidymis (internal and external), epididymal cysts, and appendix epididymis. So-called *retention cysts* are very common in the region of the head of the epididymis, especially in rams (see Fig. 5-5). They are usually up to 3 mm in diameter, contain clear fluid, and lined by epithelium similar to that of the epididymis. The paradidymis occurs proximal to the epididymis in the spermatic cord as one or several small cysts, particularly in neonates. Other cysts, seen particularly in the epididymis, can be microscopic or up to 4 cm in diameter.

Remnants of the paramesonephric ducts include the appendix testis, the uterus masculinus near the accessory genital glands, and in some cases a completely retained duct that runs beside the testis. Histologically these may have the appearance of a juvenile uterus with prominent musculature and uterine glands.

Many other disorders of development of the epididymis have minor significance. Melanosis of the epididymis occurs in rams and bulls. Adrenal ectopia is seen occasionally. Ectopic interstitial endocrine cells and ectopic interstitial cell tumors are reported in the testicular capsule, mediastinum testis, or spermatic cord of cats.

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Variation in testicular and epididymal size

The daily testicular output of spermatozoa is highly correlated with testicular volume. This is estimated by measuring scrotal circumference, for which reference ranges have been established by species or breed. Testes above this range are hypertrophied; those below the range are too small because of atrophy or hypoplasia. *Even experienced pathologists have difficulty in differentiating hypoplastic from atrophic testes in adults.* This is because there are variations in the degree of hypoplasia and, over time, hypoplastic testes may undergo degeneration. The best method to separate atrophy from hypoplasia is to document a decrease from normal testicular weight or size over time. In contrast, hypoplastic testes are smaller than normal and remain so.

In hypoplastic testes, the testis and epididymis fail to increase in size to the normal reference range at puberty (see Fig. 5-4). As such, the ratio of the weight of the testis to epididymis is similar to that of normal testes. The size of both is smaller than normal and there are histologic features of spermatogenic arrest in tubules that are smaller than age- and breed-matched controls. Testicular hypoplasia is discussed in a previous section covering testicular disorders of sexual development.

The general terminology used for a reduction in the size of the testis is to use *atrophy* for the macroscopic reduction in size and *degeneration* to refer to the histologic observations. Atrophic testes should have a ratio of testicular to epididymal weight that is reduced as the reduction in size of the testis is greater than the reduction in size of the epididymis. The basement membrane of appropriately fixed atrophic testes is thicker than normal and often has a buckled or "wavy" outline. Pathologists are usually required to make the distinction on a single observation, a diagnosis of "suspect atrophy" or "suspect hypoplasia" is not necessarily an indication of ignorance; rather, it is an indication of appropriate caution.

When one testis is larger than the other, a common assumption is that the larger testis is enlarged from neoplasia. It may be normal or hypertrophied and the contralateral testis is hypoplastic or atrophic.

Testicular atrophy and degeneration

Testicular degeneration is manifested clinically and grossly as atrophy, mineralization, and fibrosis. Microscopically, it begins as a reduction in spermatogenesis, shrinking of tubular diameter, reduction in the number of Sertoli cells, reduction in interstitial endocrine cell size, and a wavy and thickened hyaline basement membrane.

The pathophysiology is extremely complex and involves influences external to or internal within the testis. There is a seemingly endless list of potential causes from aging to toxicosis, as outlined in Box 5-1. The close interrelationship of all testicular components and especially the Sertoli cells, interstitial endocrine cells, and germ cells means that insults to any one or several of them eventually affects them all. Regulation of testicular function involves systemic and local testicular components, so the manifestation in the testis is not always bilateral or uniform within a testis. Eventually there is reduced testosterone production by interstitial endocrine cells and

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BOX • 5-1

Causes of testicular degeneration

- Advancing age
- Chemicals
  1. Chemotherapy
  2. Chlorinated naphthalenes
  3. Halogenated compounds, including hexachlorophene
  4. Nitrogen-containing compounds, including benzimidazoles, nitrofurans
  5. Metal compound toxicosis
- Epididymitis
- Heat
- Hormones
  1. Dexamethasone
  2. Estrogen
  3. Testosterone
  4. Zearalenone
- Neoplasia
  1. Pituitary tumors
- Nutritional disorders
  1. Negative energy balance
  2. Fatty acid deficiency
  3. Hypovitaminosis A
  4. Hypervitaminosis A
  5. Hypovitaminosis B
  6. Hypovitaminosis C
  7. Hypovitaminosis E
  8. Protein and amino acid deficiency
  9. Zinc deficiency
- Plants
  1. Locoweed (*Astragalus*)
  2. Lysine seeds (gossypol)
- Radiation
- Stress/corticosteroid therapy
- Trauma
- Ultrasound
- Viral infection
  1. Porcine reproductive and respiratory syndrome virus
  2. Canine distemper virus
  3. Bovine viral diarrhea virus

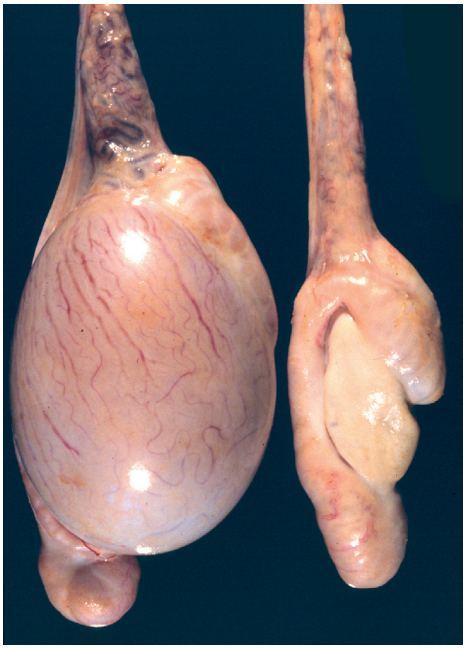

Figure 5-25 Unilateral **testicular atrophy** in a ram. The epididymis of the atrophic testis appears disproportionately large.

Figure 5-26 Unilateral **testicular atrophy** in a stallion secondary to unilateral scrotal hernia.

reduced inhibin release from Sertoli cells. It is a perplexing phenomenon that a cause acting locally in one testis can affect the opposite testis. To some extent, alteration in oxidant-antioxidant balance can explain this.

Testes undergoing *atrophy* are reduced in size (Fig. 5-25). In early or rapidly progressing degeneration, the testis is soft and flabby, lacks turgor, and the cut surface does not bulge. Wrinkling of the testicular capsule may be apparent. With ongoing loss of fluid and reduction in the germinal epithelium relative to the stroma, the result is a smaller testis of firm consistency. The substance of the testis is a darker color that is often brown (Figs. 5-26, 5-27). The epididymis is usually less affected than the testis and will appear disproportionately large. With continued degeneration and fibrosis, the testis becomes increasingly hard and tough (see Fig. 5-25). Spermiostasis in parts of individual seminiferous tubules is identified as white linear regions, especially at the mediastinum, and these may mineralize (see Fig. 5-27). Continued mineralization can result in petrification of a part of or the whole testis.

Testicular degeneration may be uni- or bilateral, and *it is assumed that unilateral degeneration is the result of a local event, whereas bilateral degeneration is the result of a systemic problem*. The testes of aged bulls frequently degenerate from the ventrum, and those from rams degenerate from the dorsum. This variable pattern of change means biopsies of testes should be interpreted with caution and respect for whether the sample is representative of the whole.

Histologic changes in degeneration (Figs. 5-28, 5-29) vary in degree, but are relatively stereotypic. In the early stages, Sertoli cells develop either fine basal vacuolation or more dramatic vacuolation of the apical cytoplasm. There also is disorganization and exfoliation of germ cells, or spermatogenic arrest at one of the many stages of the spermatogenic cycle.

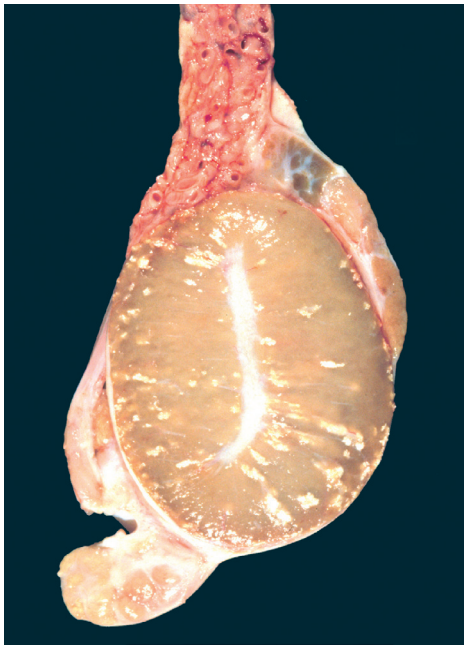

Figure 5-27 **Testicular atrophy** and resultant darker testicular color, and multifocal mineralization of seminiferous tubules in a buck.

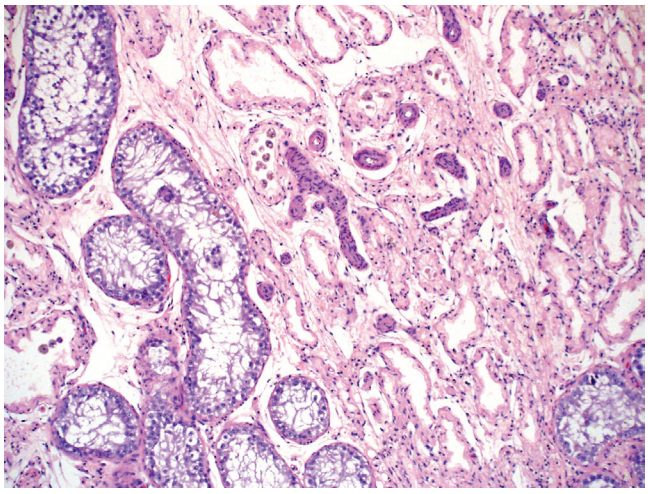

Figure 5-28 **Testicular degeneration** in a dog. Tubules are at various stages of degeneration including a Sertoli cell only pattern, reduced spermatogenesis, and buckling of basement membranes, hyalinized tubules, and depletion of both germinal and Sertoli cells. Prominent and hyalinized blood vessels are in the interstitium.

In some cases there may be failure of release of germ cells from Sertoli cells (spermiation) and spermatozoa are phagocytized by Sertoli cells.

Early changes in the germ cells include failure of maturation of spermatozoa and degeneration of spermatids; many spermatids are apoptotic and or necrotic and others produce characteristic spermatid multinuclear giant cells (Fig. 5-30). When the degeneration is more advanced, the affected areas are more extensive and degenerative changes appear in the precursors of spermatids. Depending on the insult, there may be cytoplasmic vacuolation and nuclear pyknosis, or apoptotic bodies are seen. Progression of changes results in loss of

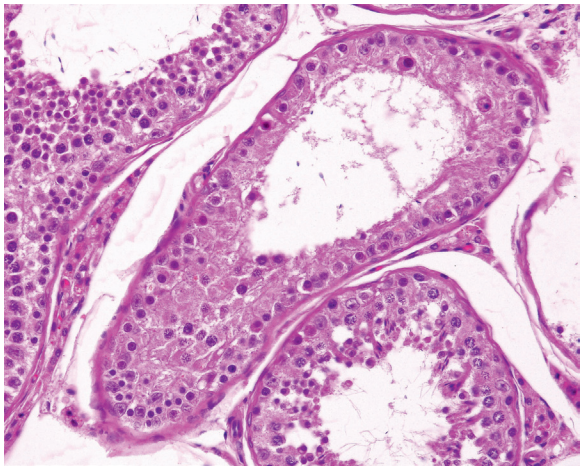

Figure 5-29 Advanced **testicular degeneration** with spermatogenic arrest in the seminiferous tubule of a dog.

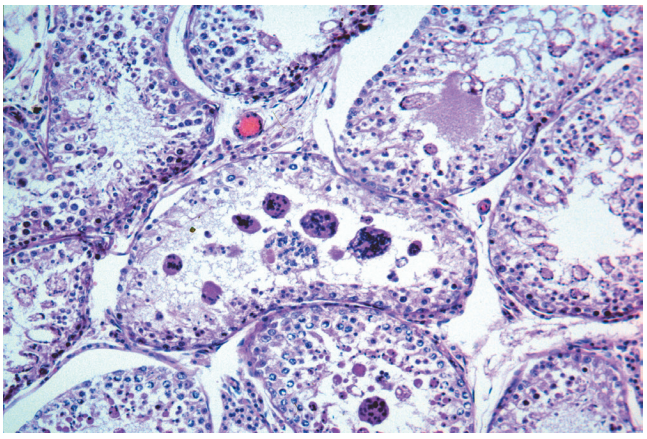

Figure 5-30 Early stages of **testicular degeneration** in a dog. Multinucleated spermatids are within the lumen.

germinal cells, and eventually, loss of even the resistant Sertoli cells (see Fig. 5-28). Basement membrane thickening is a frequent finding, and as a result, there is shrinkage and collapse of tubules. The basement membrane becomes wavy, buckled, and thickened. The periodic acid–Schiff (PAS) stain clearly accentuates the changes to the basement membrane. In ultrastructural studies of the testes of normal bulls and bulls with atrophy or hypoplasia, mean thicknesses of the basal lamina was ~0.7, 1.5, and 1.0 µm, respectively.

Once-only scrotal heating can cause the appearance of spermatid giant cells in degenerate testes and perhaps in the semen. Two types of giant cells, mononuclear giant cells probably derived from pachytene spermatocytes that fail to differentiate further, and multinucleated cells, considered to be derived from coalescence of identical spermatids, are observed histologically. Even extremely brief heating, of several minutes only, induces giant cell formation. Such giant cells are seen as early as 6 hours and as late as 7 weeks post-heating, but they seem to be most prevalent at about 1 week. The fate of these cells is unclear. They may disintegrate or pass out of the testis. In addition to giant cell formation, minor increases in testicular temperature in sheep produce a marked accumulation of spermatogonia; histologically there are many cells in which mitosis is incomplete.

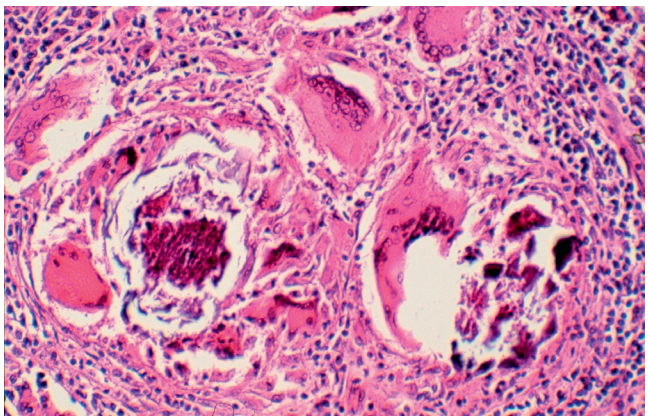

Figure 5-31 Spermiostasis and **mineralization** in a seminiferous tubule with multinucleated giant cell response and **interstitial lymphocytic orchitis**.

Granulomas can form in degenerate testes, especially where there is spermiostasis (Fig. 5-31). This, and the presence of lymphocytes and plasma cells, indicates an immune response to spermatozoa but complicates the differentiation of simple degeneration from interstitial orchitis. Alteration of interstitial endocrine cell function reduces testosterone production and a change from an anti-inflammatory to a proinflammatory cytokine profile. *Mineralization and eventually osseous metaplasia* sometimes occurs in tubules affected by spermiostasis for a long time.

Mineralization is a common sign of degeneration, and it may involve all or part of one seminiferous tubule, or whole regions (see Fig. 5-31). The basic mechanism of degeneration of the cells that make up the germinal epithelium is presumed to be via increased apoptosis.

The testis is very susceptible to changes in its local environment, such as free radical–oxidant and antioxidant balance, and cytokine signaling within the testis. A slight shift in the balance to free radical production results in degeneration and altered spermatogenesis. The intratubular compartment is particularly vulnerable to oxidative stress and free radical damage, so a change in testicular temperature, blood flow, oxygen tension, and systemic inflammation will cause degeneration. This shift in balance is believed to be responsible for testicular degeneration in the contralateral testis of a testis with degeneration from another cause, such as varicocele, stress, or systemic disease.

The testis is very susceptible to increased scrotal temperature. Both testicular and epididymal function are altered when intrascrotal temperatures increase. In the epididymis, an increase in temperature reduces mRNA expression of a spermatozoal membrane glycoprotein (CD52) in a testosterone-independent manner. An inability to maintain the testes at a temperature lower than normal body temperatures can occur with pyrexia, increased environmental temperatures, scrotal thickening and hair and wool cover, and by the presence of intrascrotal inflammation or scrotal dermatitis. Varicocele is also implicated in the failure to maintain testicular thermoregulation. The progressive degeneration of maldescended testes is believed to be the result of abnormally high testicular temperature.

Degeneration of the testes with advancing age is a recognized phenomenon. The cause is not known, and there is no clear definition of what actually constitutes age-associated degeneration. It may be secondary to degenerative vascular lesions within the testis or pampiniform plexus. A progressive alteration of the function of interstitial endocrine cells and reduced testosterone production occurs, and Sertoli cells alter their production of inhibin. It is not clear which changes are cause and which are effect. Old bulls and rams have a diffuse increase in intertubular stroma and a decreased proportion of tubular mass. Other changes include increased thickness of tunics and tubular basement membrane, increased proportion of degenerate tubules, and an apparent increased number of interstitial endocrine cells, which contain increasing amounts of lipofuscin. Older stallions have more degenerate tubules, basement membranes are thicker, and there is more collagen IV and elastin in the interstitial compartment. Myoid cells are swollen, interstitial endocrine cells appear to be increased in number, and there are lipofuscin-containing macrophages in the intertubular space. Arterioles may have a hyaline wall. Dogs have a reduced area of their seminiferous tubules that continues to decline with age. Degenerate testes usually have arterioles with a thickened wall.

Gonadotrophins are essential for the normal development and function of the reproductive tract. The pathology of *endocrine disrupting chemicals (EDCs)* is a major focus because of the potential effects of antiandrogenic and estrogenic substances on male development and reproduction. Many different EDCs are known, including those that bind to the estrogen receptor, increase aromatase expression, inhibit aromatase, are antiandrogenic, or are estrogenic. Substances in this group include lead, ethanol, diethyl stilbestrol, various insecticides including DDT, and bisphenol A. Each could adversely affect spermatogenesis and cause degeneration, although in most cases it is only mild.

There are *directly acting reproductive toxicants* in domesticated mammals. Biotransformation of such compounds can occur in the testis; those formed elsewhere may not attain significant intratesticular concentrations. The toxicant may affect any one or several of the cell types, including the interstitial endocrine cells, Sertoli cells, spermatogonia, spermatocytes, spermatids, spermatozoa, or the epididymal tissues.

Interstitial endocrine cell toxicants, as expected, affect testosterone production. Ketoconazole, ethanol, acetaldehyde, and cannabinoids are examples. Their effects include alteration of Sertoli cell function and maturation of germ cells, especially pachytene spermatocytes and spermatids.

Direct Sertoli cell toxicants will have detrimental effects on the blood-testis barrier, orientation and translocation of germ cells, hormonal and nutritional support of germ cells, and phagocytosis of residual bodies. The targets for toxicants include the actin filaments, intermediate filaments, and microtubules. Cytochalasin disrupts actin filaments, acrylamide disrupts intermediate filaments, and colchicine, vinblastine, and vincristine affect microtubules. Fortunately, many of these drugs, when used at therapeutic doses, have a temporary effect that reverses when therapy ceases. Effects seen microscopically include vacuolation or swelling of Sertoli cells and germ cell changes including increased apoptosis. Failure of spermiation can occur.

Toxicants that affect the germ cells prevent rapid mitotic division, and the spermatogonia are the major targets. Adriamycin and cyclophosphamide are examples. Damage by these compounds to the genetic composition of stem cells will also have effects on the later stages of development. Toxicants of the other germ cells are little recognized in domestic species,

although in rodents, ethyl glycol alkyl ethers affect spermatocytes, nitroimidazoles affect spermatids, and compounds that impinge on energy metabolism affect spermatozoa. Damage to various stages causes apoptosis, with a rapid uptake of the detritus by Sertoli cells. Within 48 hours, there may no longer be evidence of apoptosis—just the appearance of "maturation arrest."

Toxicants can also affect the efferent ductules and epididymis and/or the spermatozoa in transit. The difficulty with investigating efferent ductular toxicosis is separating the effect caused by alteration in testosterone concentration, and direct toxic effects. Substances that affect the efferent ductules include cyclophosphamide, methyl chloride, and reserpine. Such toxicants decrease spermatozoal concentration and cause spermiostasis, spermatic granuloma formation, and necrotic and degenerative changes to the epithelium. Several have direct effects on spermatozoa in the ducts.

There are few reports of *direct viral infection* and their effects on spermatogenesis. However, porcine reproductive and respiratory syndrome virus replicates in germ cells, alters spermatogenesis, and induces apoptosis. Bovine viral diarrhea virus is implicated in infertility. Canine distemper virus infection of dogs can cause testicular degeneration.

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Testicular hypertrophy

Enlargement of an otherwise normal testis is rarely a primary disorder. *Secondary or compensatory hypertrophy* is a unilateral condition that indicates an underlying disease in the contralateral testis. It is a well-recognized phenomenon in hemicastrates, and in hypoplasia, cryptorchidism (see Fig. 5-3), or atrophy of the contralateral testis (see Fig. 5-25). In rams and bulls, hypertrophy occurs when the unilateral condition is present during the peripubertal period, and with increased FSH production. The increase in size can be double and is due to an increase in the diameter and length of the seminiferous tubules with more numerous and larger Sertoli cells and more germinal cells per Sertoli cell. Hemicastration of prepubertal boars, especially in those younger than 3-4 months, results in dramatic hypertrophy of the contralateral testis.

The presence of *dilated cystic remnants and pseudocysts* can also cause, or be confused with, enlargement of a testis. Occlusion of the efferent ductules can lead to dilation of the rete and mediastinum testis and appear as testicular enlargement, although the thickness and fibrous nature of the testicular capsule makes sudden enlargement of the testis less likely. Adhesions and thickenings of the vaginal tunic can also appear clinically as testicular enlargement. To the unsuspecting, lesions of the scrotum or its contents are mistaken as testicular enlargement; hydrocele, epididymitis, or the presence of spermatic granulomas are examples.

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Inflammation of the testis and epididymis

Orchitis

Apart from bulls in areas endemic for *Brucella abortus* or tuberculosis, and in some cases of canine epididymitis, orchitis is a rare and sporadic disease in domesticated animals. *The vast majority of cases diagnosed clinically as orchitis are actually epididymitis* (see later). Focal accumulations of lymphocytes are occasionally seen in the testes of most species as incidental findings. Lymphocytic (or nonsuppurative) inflammation is seen in some infertile animals; an immunologic pathogenesis is invoked as immunization of guinea pigs and bulls with spermatozoa induced inflammation of the rete testes especially. Efferent ductules are also involved experimentally.

Orchitis as the primary and severe disease has historically been attributed to brucellosis or tuberculosis. Tuberculous orchitis is a multifocal granulomatous disease that is much less common now because of eradication in many countries. Brucellosis is similarly reduced in prevalence. *Brucella abortus* (bulls), *Brucella suis* (pigs), *Brucella canis* (dogs), and *Brucella melitensis* (goats) can cause orchitis as a dominant change. However, epididymitis is often the main manifestation.

Orchitis is traditionally divided into 3 major categories: interstitial orchitis, intratubular or granulomatous orchitis, and necrotizing orchitis.

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Interstitial orchitis. Interstitial orchitis may not be recognized macroscopically, but histologically there are lymphocytes in the interstitial stroma, with concurrent or subsequent fibrosis. In bulls, small clusters of lymphocytes are frequently observed adjacent to seminiferous or rete tubules or efferent ductules of otherwise normal testes. In stallions, interstitial perivascular lymphocytic foci are particularly common and occur in areas of degeneration. Lymphoid aggregates are frequently seen in Beagle dogs used as laboratory animals. Foci of lymphocytes in cats are considered an age-associated change.

Intratubular orchitis. Intratubular orchitis is inflammation focused on the seminiferous tubules. Some cases result from *ascending infection* but in others there is no epididymitis to confirm this. Alternative explanations include a breakdown of the blood-testis barrier allowing agents into the tubules, or spermatozoal antigens leaking into the interstitium. Macroscopically, there are solitary or multiple white-yellow foci of up to 1 cm diameter. Histologically, the tubule outline is retained in the affected area, but the seminiferous epithelium is either degenerate or obliterated and replaced by macrophages and multinucleated giant cells that surround neutrophils and debris (Fig. 5-32). In some cases, the reaction is predominantly lymphocytic, suggesting an autoimmune pathogenesis. The pathogenesis of the granulomatous orchitis is comparable to spermatic granuloma formation in the epididymis. Sertoli cell hyperplasia and mineralization may accompany these changes.

Necrotic orchitis. Necrotizing orchitis is characteristic of *brucellosis* but may result from other infections, or conditions causing severe trauma or ischemia of the testis. Severe periorchitis may reduce blood supply to the testis so that it becomes a necrotic mass encased within the markedly thickened tunics. Necrotic areas are dry, yellow, often laminated, and slightly mineralized. The histologic picture is coagulative necrosis bordered by fibrosis and inflammatory cells. Abscessation and fistulation through the scrotum may accompany necrotizing or other forms of orchitis.

Orchitis in bulls. In bulls, many viruses have been isolated from testes or semen. Histologic changes are seldom found. Persistent infection with bovine viral diarrhea virus results in spermatozoal defects but no distinct histologic lesions in the testis. Severe interstitial orchitis and testicular degeneration and inflammation of spermatic arteries occur in bovine malignant catarrhal fever (alcelaphine herpesvirus 1 and ovine herpesvirus 2). In experimental bluetongue virus infection in bulls, interstitial orchitis accompanies arteritis. Clinical orchitis and aspermatogenesis were listed as findings in bovine enterovirus 1 infection, but lesions are not described. A focal nodular orchitis is reported in lumpy skin disease (lumpy skin disease virus) of bulls.

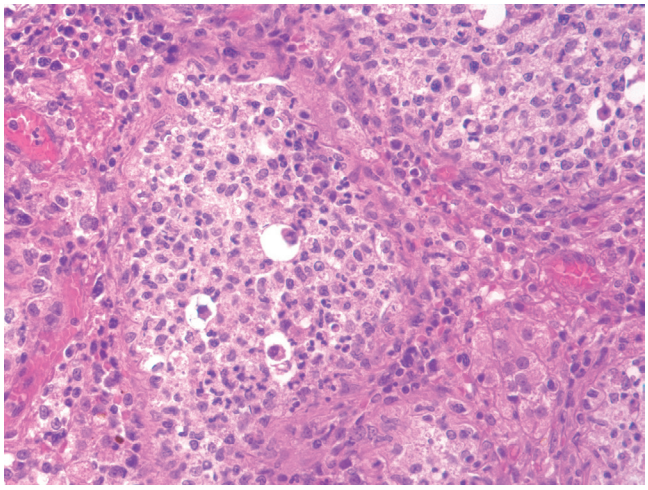

Figure 5-32 Severe intra-tubular **neutrophilic necrotizing orchitis** in a dog.

Orchitis in bulls is similar grossly and histologically, regardless of the causative bacterium. The best descriptions are of *Brucella abortus* infection in endemic regions. In most instances the orchitis is acute and severe. It may be unilateral but affected animals are sterile. The scrotum swells and is hot and doughy as a result of inflammatory changes in the tunics and to a lesser extent in the epididymis. Swelling of the testis is limited by the inability of the testicular capsule to stretch, and any swelling constricts venous and then arterial flow causing infarction. The cavity of the vaginal tunics distends with fibrinopurulent exudate. Scattered yellow foci of necrosis coalesce to produce total testicular necrosis. Sequestration by inflammation and thickening of the tunics follows. Sometimes the necrotic parenchyma liquefies and the organ then is a pus-filled cavity surrounded by a thick connective-tissue capsule. Rupture may occur but is unusual.

Microscopically, the inflammation of the tunics results in extremely dense adhesions between the parietal and visceral layers. Within the testes, the infection appears to progress along the lumen of the seminiferous tubules. The seminal epithelium becomes necrotic and desquamates. Large numbers of the organisms are visible in the lumen. At the early stage, neutrophils, macrophages, and lymphoid cells are in the interstitial tissues and form cuffs about the tubules. The tubules and the interstitial tissues then become necrotic. There is often focal necrotizing epididymitis complicated by the development of spermatic granulomas.

Tuberculous orchitis in bulls is an uncommon lesion, even in areas of endemic infection. The granulomatous response to the tubercle bacilli is similar to the granulomas that occur to spermatozoa. Involvement of the testis may be either miliary or regional. In the miliary form, small or large caseous and mineralized foci are irregularly scattered throughout the testes but may spare the epididymis entirely. The path of infection is probably intratubular from a primary epididymal lesion.

Other bacteria causing orchitis in bulls, sometimes with overt abscessation, include streptococci, staphylococci, *Trueperella pyogenes*, *Escherichia coli*, *Histophilus* spp., *Salmonella* spp., *Actinomyces bovis*, *Actinobacillus* spp., and *Nocardia* spp. In nocardiosis especially, the lesions are at first nodular but ultimately transform the whole testis into an abscess, the capsule of which is the vaginal tunic.

Infection of bulls with *Chlamydophila* spp. causes orchitis, and in field cases, focal granulomatous lesions are observed. The spontaneous occurrence of orchitis and epididymitis caused by *Mycoplasma* spp. infection is reported.

Orchitis in boars. Viral infection of the testis and shedding in the semen of boars is identified in many, but inflammation in natural disease is not well documented, or is not reported. Intratesticular inoculation is used in an experimental setting, and this overwhelms natural defences and adds local trauma as a complication. Experimental orchitis and epididymitis is reported in porcine rubulavirus (a paramyxovirus responsible for the disease "blue eye") infection. The virus targets the head

of the epididymis, where it causes interstitial inflammation and spermatic granulomas. Interstitial fibrosis is seen in animals that recover. Suid herpesvirus 1 infection (pseudorabies, Aujeszky's disease) may cause edema of the scrotal region; intratesticular inoculation results in exudative periorchitis. Porcine parvovirus 1, porcine reproductive and respiratory syndrome virus, and porcine circovirus 2 replicate in the reproductive tract and may cause testicular degeneration.

Orchitis caused by *Brucella suis* results in multiple abscesses rather than confluent necrosis. Some cases have fibrinopurulent and hemorrhagic periorchitis. Abscessation develops in the epididymis as well as in the testis; there is central caseation surrounded by a zone of epithelioid macrophages, and these in turn by a broad connective-tissue capsule and lymphocytes and plasma cells.

In some tropical countries, orchitis caused by infection with *Burkholderia pseudomallei* occurs in boars and other domestic mammals. Lesions can occur in the vesicular glands, prostate, and other organs. Extreme enlargement of the testis caused by purulent inflammation may occur. The main histologic lesion is multifocal necrosis with marked lymphocytic inflammation and encapsulation by much fibrous connective tissue. Severe testicular degeneration accompanies orchitis. Other organisms isolated from boars with orchitis include *Trueperella pyogenes, Streptococcus zooepidemicus, Streptococcus equisimilis*, and *Salmonella* spp.

An inbred strain of Duroc boars developed a high prevalence of lymphocytic interstitial orchitis suggesting a genetic predisposition. The orchitis caused degeneration of the seminiferous tubules and predominantly unilateral testicular atrophy.

Orchitis in stallions. In stallions, mild interstitial orchitis is common and incidental. Similar lesions may be part of generalized vascular involvement in equine viral arteritis. Infarcts may also occur in equine infectious anemia. Orchitis can occur as part of systemic disease, and is reported in glanders (*Burkholderia mallei*), and as an acute suppurative, sometimes abscess-forming orchitis in infection with *Salmonella abortus-equi*, *Streptococcus equi*, and *Streptococcus zooepidemicus.* Focal lesions attributed to the migrating larvae of *Strongylus edentatus* are reported in the testis, tunics, and epididymis, especially of young horses. Cryptorchid testes are more commonly affected. Hemorrhagic 2-mm wide tracts containing the migrating larvae are seen. The histologic lesions are initially hemorrhagic and then become eosinophilic. *Halicephalobus gingivalis* can cause granulomatous orchitis as a consequence of systemic spread. A pseudocyst is reported in a horse as a sequel to fibrinonecrotic orchitis. The lesion was associated with trauma, and secondary infection with *Streptococcus zooepidemicus* occurred.

Testicular rupture, hemorrhage, and orchitis can occur with trauma to the testis, such as when a stallion is kicked while mating a mare. Spermatic granulomas in the testis occur secondarily.

Periorchitis in horses occurs as part of generalized septic disease, peritonitis, and as a complication of trauma, penetrating injury, or surgery.

Orchitis in small ruminants. In rams, nodular orchitis occurs in sheep pox in a similar fashion to lumpy skin disease in bulls. Chronic interstitial orchitis is reported in rams infected with the ovine lentivirus maedi-visna virus. The most common causes of orchitis are bacteria that also cause epididymitis. It is unusual to find orchitis in the absence of epididymitis. Sporadic testicular abscesses result from infection with *Trueperella pyogenes* and *Corynebacterium pseudotuberculosis.*

In bucks, caprine arthritis-encephalitis virus is found in semen and in the testis and epididymis but without lesions. Orchitis may result from infection with *Brucella melitensis*. It can be severe enough to induce a fibrinonecrotic disease. Orchitis also occurs in breeding goats as a component of besnoitiosis.

Orchitis in dogs and cats. Dogs with canine distemper virus infection develop intranuclear and cytoplasmic inclusions in Sertoli cells. The majority of seminiferous tubules degenerate, and inflammation occurs in some tubules.

Orchitis is seen with bacterial epididymitis, where there is retrograde spread from the epididymis. *Escherichia coli, Proteus vulgaris*, and other coliforms are usually responsible. An acute inflammatory response in either the epididymis or testis is usually necrosuppurative, with the formation of one or more abscesses (see Fig. 5-32). The vaginal tunic is involved by extension, and fistulation through the scrotal skin to the exterior may occur. Dogs will traumatize their scrotum and produce a fistula. Acute inflammation usually is centered on the ducts, with degeneration and desquamation of the epithelium, and edema and neutrophils in the surrounding stroma. Healing occurs by scarring. With time, the affected testis becomes firm, small, and irregular. Lymphocytes and plasma cells predominate and fibrosis is well developed.

Other bacterial causes of orchitis in dogs include *Brucella canis* and *Burkholderia pseudomallei*, both of which cause epididymitis (see later). A familial occurrence of interstitial, lymphocytic orchitis, associated with testicular atrophy and reduced fertility, was observed in inbred Beagle dogs with lymphocytic thyroiditis; immune factors were implicated. Fungi such as *Blastomyces dermatitidis* can cause orchitis as part of systemic disease. Protozoal orchitis caused by *Leishmania* spp. is reported in dogs. Penetrating wounds of the scrotum affect the scrotal contents including the testis.

Orchitis in **cats** is very rare. Feline infectious peritonitis virus can induce a primary orchitis (Fig. 5-33); however, periorchitis is the usual manifestation. Orchitis can be a sequel to traumatic injury to the scrotum.

Orchitis in camelids. Orchitis is uncommon in camelids. Septic orchitis from *Streptococcus equi* subsp. *zooepidemicus* is reported in an alpaca. Camels are susceptible to *Brucella abortus* and *Brucella melitensis*, and some develop orchitis.

Epididymitis

Inflammation of the epididymis is very common. Regardless of cause, damage to the epididymal duct results in a response to spermatozoa and other luminal contents, spermatic granulomas, and subsequent development of chronic epididymitis. The exception is in prepubertal animals in which there are no spermatozoa; in these cases, true abscesses occur. Epididymitis in the absence of sperm granulomas is possible in adults, but it usually is a subclinical or early event.

Epididymitis is usually *infectious,* and infectious disease frequently causes a spectrum of lesions, including inflammation of the accessory genital glands. The effects of epididymitis are usually more dramatic than prostatitis, vesicular adenitis, or ampullitis, and these are often overlooked. *Sterile epididymitis* with spermatic granulomas does occur in congenital ductal disorders of sexual development, adenomyosis, trauma, and reflux of urine.

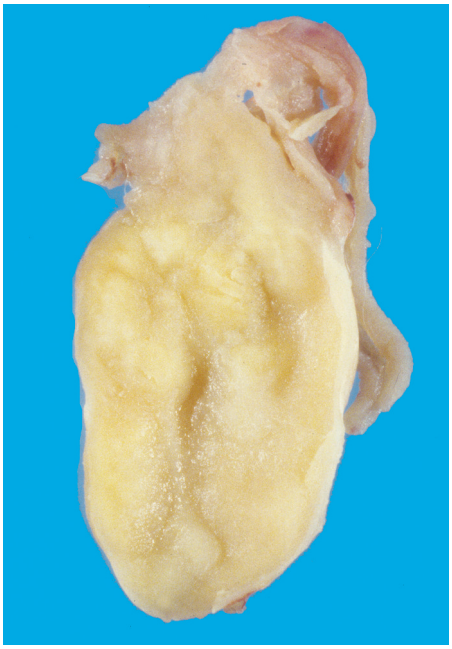

Figure 5-33 Pyogranulomatous orchitis from feline infectious peritonitis virus infection in a cat.

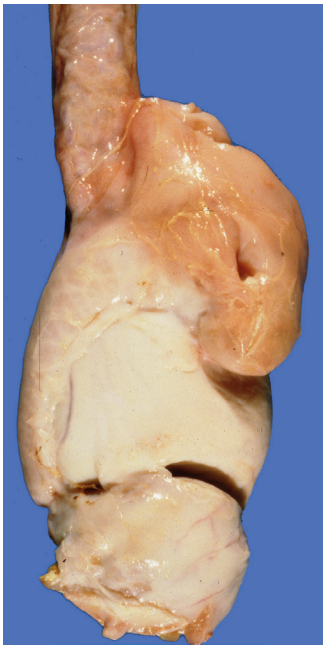

Figure 5-35 Chronic epididymitis in a ram, with marked epididymal enlargement, fibrosis of the tunics, and testicular atrophy. *Brucella ovis.*

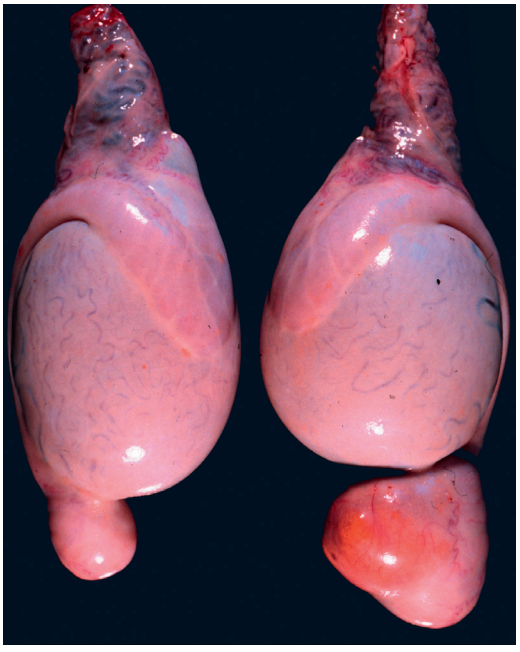

Figure 5-34 Unilateral epididymitis of the tail of the epididymis in a ram. Spermatic granuloma is visible. *Brucella ovis.*

Bacteria cause most infections of the epididymis. Many viruses replicate in the epididymis but seldom induce epididymitis. Any agent causing orchitis is capable of inducing epididymitis.

Primary infection with *Brucella* spp. in each species results in epididymitis. *B. suis, Brucella ovis* (Figs. 5-34, 5-35), *B. melitensis* and *B. canis* are especially virulent for the epididymis. Infection is systemic, beginning with contact of mucous membranes, spread throughout the body, and localization in the epididymis and accessory genital glands. Retrograde infection from the prepuce and via the ducts is theoretically possible.

Almost all species develop infection of the epididymis by the ascending route (with the exception of brucellosis). This was studied in the ram, where *Actinobacillus seminis* and *Histophilus somni* are classic isolates. Preputial organisms migrate to the accessory genital glands and infect the epididymis by retrograde movement. The privileged environment of the lumen of the epididymal duct allows the organisms to infect the organ and incite damage. The subsequent formation of spermatic granulomas means that the reproductive potential of the affected side is lost. Complete return to normal is rare. Dogs with epididymitis will self-traumatize the scrotum (see Fig. 5-10). Endotoxin-producing bacteria such as *Escherichia coli* further complicate epididymitis by causing systemic illness.

Prevention of infection of the epididymis is reliant on innate mechanisms, particularly isolation from exposure to infectious organisms, and constant flushing with antimicrobial substances in fluid. Microbial pattern recognition molecules, such as toll-like receptors, are present on the epithelial cells of the epididymis and other parts of the tract. Stimulation of local immunity to prevent epididymitis is unlikely. The epididymis has no natural local immune system of antigen receptors, nor known recirculation of immunocytes, and no local plasma cell population. Aggregates of lymphocytes occasionally occur in otherwise normal animals. After infection, the epididymis must develop a local immune system, but unfortunately the damage is usually so extensive, and the sequel so severe, that the response is too late. Even so, the epithelial cells do have the ability to express MHC I and II, and lymphocytes and plasma cells can be recruited after challenge.

Direct infection of the epididymis by penetrating injury is a rare event. Secondary infection from periorchitis or peritonitis is a possibility.

Once initiated, the course of epididymitis is variable. The acute stage, with edematous enlargement, precedes abscess and spermatic granuloma formation, sometimes with

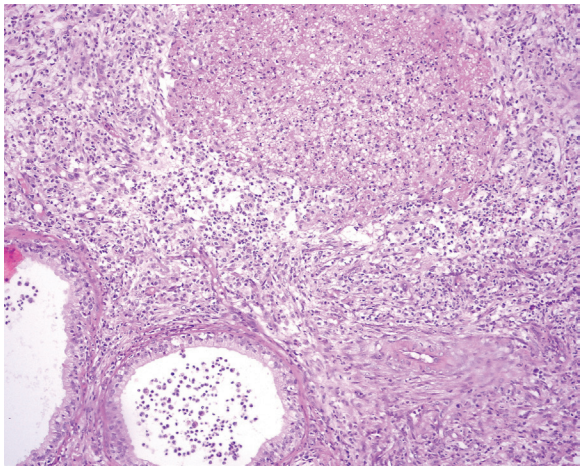

Figure 5-36 Microscopic changes in **necrosuppurative epididymitis** in a dog.

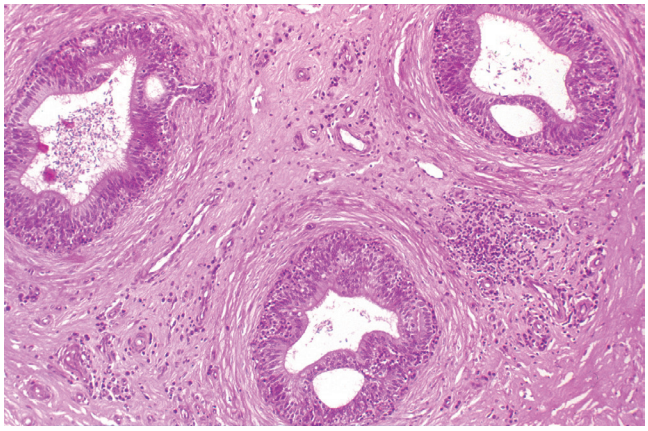

Figure 5-37 **Chronic epididymitis** in a ram, with interstitial fibrosis, epididymal epithelial hyperplasia, and intraepithelial lumina formation.

perforation, periorchitis and peritonitis, and increasing fibrosis (see Figs. 5-10, 5-35).

Macroscopically, increased epididymal size and dissymmetry in shape are apparent, especially in unilateral cases in comparison with the contralateral side. Fibrinous and then fibrous adhesions may be present between affected epididymis and adjacent tunics. Consistency will depend on duration of inflammation and the development of spermatic granulomas. With time, the amount of fibrous tissue produced is dramatic (see Fig. 5-35), both within the epididymis and between the tunics. The epididymal duct may not be recognizable or visible as dilated spaces with inspissated spermatozoa in the lumen. With mineralization of the spermatozoa, hard "sperm stones," the end products of spermiostasis, may be present within such ducts. Concurrent testicular atrophy will result in the epididymis appearing disproportionately large in relation to the testis (see Fig. 5-35).

Intraluminal fibrin, neutrophils, and spermatozoa dominate the microscopic changes in the initial phase of bacterial infection. The epithelium disintegrates and interstitial lakes of neutrophils with fibrin form (Fig. 5-36). Macrophages, and multinucleated giant cells, many of which contain spermatozoa, are found later in the course of disease. Other features of spermatic granuloma, including a prominence of interstitial lymphocytes and plasma cells, become apparent (Figs. 5-37, 5-38). Epithelial hyperplasia, with the development of intraepithelial lumina (see Fig 5-37), occurs in most domestic species with epididymitis. Such lumina also occur in noninflammatory lesions. In chronic epididymitis, there may be squamous metaplasia of epithelium. Progressive fibrosis is usual.

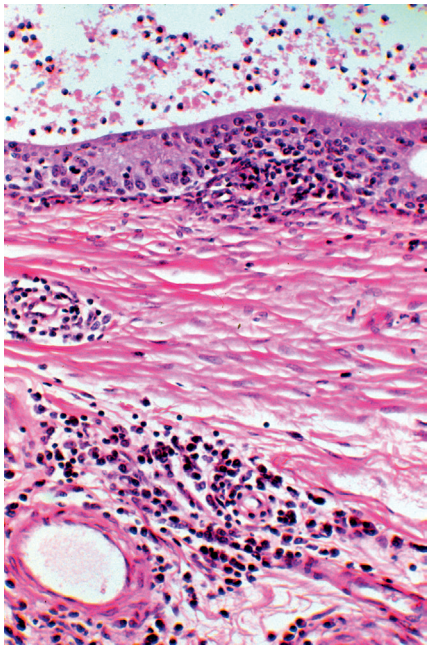

Figure 5-38 Microscopic appearance of **chronic epididymitis** in a ram showing intraluminal neutrophils, interstitial fibrosis, and many lymphocytes and plasma cells, especially around vessels.

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Epididymitis in bulls. Viral causes of epididymitis are rare. Bulls in Kenya and South Africa developed a specific infectious epididymitis, called epididymitis-vaginitis ("epivag"). Lesions consist initially of soft swelling of the epididymis with subsequent enlargement and fibrosis. Other lesions include "abscess" formation, tunic adhesions, ampullitis, vesicular adenitis, and testicular degeneration. Sometimes, however, the vesicular glands only are affected. The possible role of bovine herpesvirus 4 in the pathogenesis of "epivag" is discussed in Vol. 3, Female genital system.

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Brucella abortus rarely causes epididymitis in the absence of orchitis. *Actinobacillus seminis*, a frequent cause of epididymitis in rams, has been isolated from the semen of a bull with bilateral epididymitis. Epididymitis is observed in bulls with vesicular adenitis induced by inoculation of *Mycoplasma bovigenitalium*, but the role of mycoplasmas and chlamydias in causing epididymitis awaits clarification. Epididymitis may accompany orchitis, periorchitis, and testicular degeneration in cattle, horses, sheep, goats, and dogs infected with *Trypanosoma brucei*.

Epididymitis in boars. *Brucella suis* infection is a classical cause of epididymitis, and the lesions are variable. Single or multiple "abscesses" are frequent in the epididymis, but less so in the testes, which may be enlarged or atrophic. Enlargement of the vesicular glands caused by localization of *B. suis* may also occur, and abscessation, perhaps seen only microscopically, occurs in the vesicular glands and prostate and bulbourethral glands.

Epididymitis in stallions. In the stallion, migrating strongyle larvae are implicated as a cause of epididymitis and spermatic granuloma of the epididymis; adenomyosis is a further cause. Rare sporadic cases of bacterial epididymitis are reported with *Streptococcus zooepidemicus* isolated from such cases.

Epididymitis in small ruminants. Epididymitis is of particular importance in rams, in which it is a frequent and serious cause of reduced fertility. Although either *Brucella ovis* or *Actinobacillus seminis* are usually responsible, many other bacteria, such as *Histophilus somni*, *Mannheimia haemolytica*, *Escherichia coli*, and *Trueperella pyogenes*, are isolated from sporadic cases of epididymitis. Whereas *Brucella ovis* is a cause of epididymitis in mature rams, other gram-negative pleomorphic organisms are commonly cultured from epididymitis in virgin rams, suggesting the existence of two separate disease entities.

Ovine epididymitis caused by *Brucella ovis* is an important cause of reduced fertility in many countries and is studied extensively. Progression of the infection is very slow, from a local infection persisting in the exposed mucus surface for 1 month, to a regional one involving adjacent lymph nodes, leading to bacteremia. The bacteremic stage subsides after about 2 months, but organisms localize in the genital tract, spleen, kidney, and liver, where they persist for an indefinite period. Following experimental infection, neither gross nor microscopic lesions are seen in organs other than genitalia.

In the vast majority of epididymides with lesions caused by *Brucella ovis*, the epididymal tail is involved, and lesions in this location probably occur in all epididymides infected with this organism. Initial localization of the bacteria produces edema, and lymphocytes and macrophages appear. Later, neutrophils appear. Early epithelial changes include degeneration and then hyperplasia, with the formation of intraepithelial lumina (see Fig. 5-37). At the same time there is increasing fibrosis in interstitial areas (see Figs. 5-37, 5-38). The combination of inflammation, fibrosis, and epithelial hyperplasia obstructs the lumen and causes spermiostasis. These changes can develop over many months, and large numbers of organisms are in the ejaculate. Subsequent events depend on the extravasation of spermatozoa and formation of spermatic granulomas. The tail of the epididymis in these cases may be enlarged 4-5 times (see Fig. 5-35), and the lesion is often bilateral. If the inflammatory reaction and extravasated spermatozoa enter the cavity of the vaginal tunic, adhesions will result and testicular degeneration increases. Unlike brucellosis in the bull, there is seldom a primary orchitis. Lesions in the deferent duct similar to those in the epididymis may occur, but there is no sperm stasis or leakage. There is pronounced epithelial hyperplasia, with thickening and folding of the wall, and the lamina propria contains many lymphocytes, plasma cells, and histiocytes. Many rams do not develop detectable gross lesions or they develop them only late in the course of the disease. Identification of *B. ovis* in histologic sections is difficult, but is aided by immunohistochemistry.

Actinobacillus seminis and related strains of the so-called gram-negative pleomorphic organisms also induce epididymitis. Both *H. somni* and *A. seminis* are temporarily resident in the prepuce and become opportunistic pathogens by ascending infection. This usually occurs at puberty, when there are elevated levels of gonadotrophin releasing hormones. The pathogenesis of *E. coli* epididymitis in rams probably is similar. Typically, these are severe infections in young rams, and there may be severe and diffuse periorchitis. In epididymitis caused by *Actinobacillus seminis*, there is fibrinosuppurative and necrotic inflammation of one or both epididymides, and these may fistulate through the scrotal wall. Histologically, the initial epididymal lesion is similar to that of *Brucella ovis*. In the chronic form of the disease seen in older rams, the epididymides are large and fibrotic, and the testes are atrophic (see Fig. 5-35). The vesicular glands also may be affected. Experimental inoculation of rams by various routes with *Actinobacillus seminis* has shown that part of or the entire genital tract may become infected, but that the epididymis is most constantly involved.

Epididymitis is less studied in **bucks** than in rams. *Brucella melitensis*, *Actinobacillus seminis*, *Staphylococcus aureus*, *Escherichia coli*, or *Pseudomonas* spp. may be isolated from lesions, and there is a report of possible *Brucella ovis* epididymitis in an Angora goat.

Epididymitis in dogs and cats. Viral epididymitis is rare but it reported in canine distemper virus infection. Cytoplasmic and intranuclear inclusions are present in the epithelial cells and there is a lymphocytic interstitial epididymitis. Eosinophilic cytoplasmic bodies are normally present in the head of the epididymis and should not be confused with viral inclusion bodies; immunohistochemistry will differentiate these inclusions.

In male dogs infected with *Brucella canis*, there is epididymitis, prostatitis, scrotal dermatitis, and testicular atrophy. These changes can be unilateral. Infected animals are bacteremic and the organism can persist in tissues (e.g., the prostate) for many months. Recovery can eventually occur and recovered dogs are immune to reinfection. Venereal transmission to females by infected males can occur, although the organism is not consistently isolated from semen. Scrotal swelling is apparent 1-2 weeks after experimental intravenous inoculation, or 3-5 weeks after oral infection. Such swelling is from fibrinopurulent exudate in the cavity of the vaginal tunics. Scrotal ulceration is the result of persistent licking of the scrotum caused by the pain of epididymitis. Testicular lesions are seldom if ever observed but testicular necrosis (as observed in the bull) may occur rarely, and there is concurrent marked fibrous thickening of tunics.

Microscopically there is coagulative necrosis from necrotizing vasculitis and associated thrombosis, and a predominantly lymphoid response peripherally. More frequently, however, there is interstitial epididymitis and prostatitis, and testicular

atrophy. Lymphocytic inflammation of epididymal stroma is variable. Fibrosis may be extensive but, in contrast to brucellosis in other species, obliteration or stricture of ducts is unusual. Neutrophils and macrophages are present in the epididymal duct. In chronic cases, there is marked enlargement of the epididymis, especially the tail, with involvement of the deferent duct. The ejaculate of male dogs with chronic brucellosis contains inflammatory cells, abnormal spermatozoa, and spermatozoa agglutinins. The resulting infertility may be mediated by isoimmune reactions resulting from the heightened nonspecific phagocytic activity of cells attracted to the sites of bacterial growth in the epididymis. *Brucella suis* also may cause spontaneous granulomatous epididymitis and prostatitis in the dog.

Escherichia coli or other gram-negative bacteria cause most sporadic cases of canine epididymitis (see Fig. 5-36). The epididymitis often has concurrent severe systemic disease from endotoxemia. Scrotal swelling and mutilation are common. The range of lesions is similar to those of canine brucellosis, although the lesions are usually more severe.

Following infection with *Burkholderia pseudomallei*, dogs develop pyrexia, lethargy, scrotal swelling, edema of one or more limbs, and lameness. Macroscopically, the epididymides are enlarged 3-4 times normal, are firm and hemorrhagic, and may contain small necrotic foci. The testis and deferent duct may also be involved.

Mycoplasma canis can cause urinary tract infection in dogs, with subsequent purulent epididymitis and prostatitis.

Mycotic epididymitis caused by *Rhodotorula glutinis* or *Blastomyces dermatitidis* produces granulomatous epididymitis with a reaction pattern similar to disease in other tissues. The complication of spermatic granulomas adds to the granulomatous nature of the disease.

Ascending epididymitis is exceedingly rare in **cats**. Epididymitis can occur in feline infectious peritonitis.

Camelids develop epididymitis rarely. Camels are susceptible to *Brucella abortus* and *Brucella melitensis*, and develop orchitis and epididymitis.

Circulatory disturbances

The spermatic artery is long because of the coiled portions of the pampiniform plexus proximal to the testis. The degree of coiling is marked in ungulates and the spermatic artery is several meters long. Testicular blood flow is low in relation to metabolic needs, and hypoxia and oxidative stress develops quickly if increasing testicular temperature increases metabolic demand or if blood flow is impaired. By the time the artery penetrates the testicular capsule, pulsatile flow is almost eliminated and the structure of the vessel changes. The diameter enlarges, the wall becomes thinner, and the elastic fibers are reduced. Increased intratesticular pressure will reduce blood flow dramatically.

The interstitial tissue of the testis has abundant *lymphatics*. In addition to the usual role in fluid exchange, they probably assist in transportation of hormones between interstitial endocrine cells and the tubules. Edema of the testis occurs after trauma and is a frequent early change in orchitis. Although the testicular capsule is relatively indistensible, some enlargement can occur. With edema, there is separation and dilation of tubules, diffuse vacuolation of germinal epithelium, and dilation of lymphatics.

The walls of arterioles become thicker and hyaline in wedge-shaped areas of fibrosis in the testes of old bulls, but the precise cause of this lesion is not clear. In old dogs, arteries and arterioles in regions of testicular degeneration have thickened hyaline walls. Initial lesions occur in the testicular capsule and parenchyma, but the artery in the spermatic cord is affected too. Focal areas of ischemia and infarction may occur with severe vascular lesions. Atheromatous change is rare; in dogs this change may indicate hypothyroidism or diabetes mellitus.

Thrombosis of testicular arteries, usually of unknown cause, is seen occasionally in bulls. Such thrombi are present in both the parenchyma and tunics and may be partially mineralized and sometimes occluding. The degenerative changes in seminiferous tubules are usually mild, however. In experimental *Trypanosoma vivax* infection in sheep, thrombosis of testicular vessels probably contributes to testicular degeneration. Subsequent infarction and necrosis may sometimes occur. Venous thrombosis was observed in the testes of rams in isolated accounts. The thrombi were solitary and laminated. Some affected rams had a concurrent varicocele; testicular degeneration was mild.

Inflammation of the testicular artery occurs in the horse. The known causes are migrating strongyle larvae and equine arteritis virus infection, but a cause was not found in many cases. The usual lesions in testicular tissue include focal aggregates of lymphocytes and degeneration of seminiferous tubules adjacent to the inflamed arteries and arterioles. The inflammatory reaction is rarely severe enough to cause thrombosis and infarction. Horses infected with equine arteritis virus may have acute necrotic vasculitis, edema, and hemorrhage. Chronic cases will have lymphocytic vasculitis and perivasculitis.

A striking vasculitis with marked interstitial epididymitis, orchitis, and testicular degeneration occurs in malignant catarrhal fever in buffaloes and bulls. Dogs may develop vasculitis as part of a localized or generalized polyarteritis, and it may occur in juvenile systemic necrotizing polyarteritis/vasculitis ("Beagle pain syndrome").

Occlusion of the testicular artery with resulting ischemia of the testis may result from torsion (see Figs. 5-18, 5-19), contusion of the spermatic cord, inappropriate placement and/or hypotension during surgery, or the use of an emasculatome for castrating young lambs and calves. Experimentally, destruction of germinal epithelium can be demonstrated after ischemia of more than 1 hour. Necrosis of testicular parenchyma follows after 4-6 hours, although spermatozoa are relatively resistant to lysis and may retain their staining characteristics for weeks or months. The outermost part of the testis may survive with diffusion of oxygen and nutrients from the vaginal tunics. Islets of seminiferous tubules at the capsule (Moskoff's islets) may survive, and regeneration occurs during the ensuing months. As the regenerated tubules lack a normal drainage system, there is spermiostasis and ultimately degeneration. In addition and following ligation of the spermatic artery in prepubertal rams, revascularization of the testicular capsule occurred by penetration of capillaries from the epididymal arteries.

Torsion *of the testis is rare unless there is incomplete descent*. The stallion appears to be the exception, as spontaneous torsion of an intrascrotal testis is a recognized cause of "colic." In other species, such as cats, there are individual reports. In dogs especially, testicular neoplasia is often also present, to provide sufficient weight to maintain the torsion. The usual clinical presentation is acute abdominal pain, and the testis is

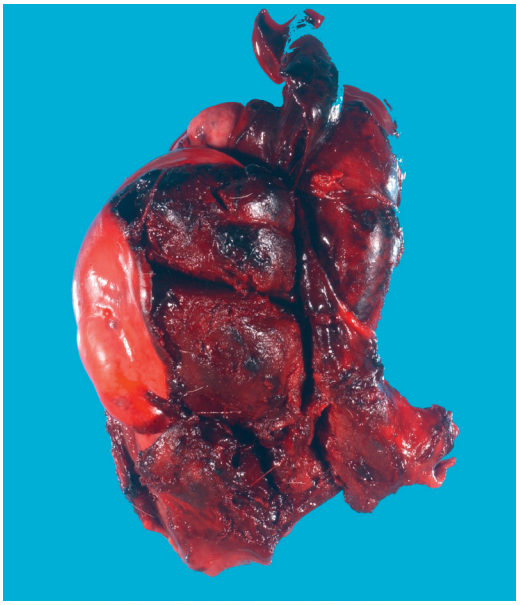

Figure 5-39 Massive testicular hemorrhage from trauma in a ram.

dark red to black as a result of venous infarction, and is sometimes unidentifiable as testis. Spontaneous torsion of the cryptorchid testis of boars is seen commonly at slaughter (see Fig. 5-18). Torsion with complete ischemia and infarction will cause complete loss of spermatogenesis of the affected testis. Correction of torsion in laboratory animals and humans can save the testis, but some continue to be aspermatogenic even if infarction does not occur. Interstitial endocrine cells and Sertoli cells retain their ability to function, but reactive oxygen species and proinflammatory cytokines such as TNFα and IL-1α may induce germ cell apoptosis and loss, and chemotaxis of neutrophils. Experimental unilateral torsion in pigs leads to degeneration in the contralateral testis, suspected to be from lower blood flow and then reperfusion and oxidative injury.

Testicular hemorrhage occurs with trauma or with some forms of necrosis of the testis. Trauma from fighting (Fig. 5-39) or motor vehicle accidents is the usual cause.

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Neoplasms of the testis and epididymis

Testicular neoplasms are most commonly found in the dog. There is no satisfactory explanation for this, but intact pet dogs live a long time and are watched closely. Male cats tend to be castrated early and fewer intact males live to old age. Neoplasms arise in all species sporadically, and with the exception of the dog, it is possible to predict the histologic type of neoplasm based on species and age. Seminoma is the common tumor of the aged horse, and teratoma is more common in the young. Boars, rams, bucks, and cats rarely get testicular neoplasms, and both seminoma and Sertoli cell tumor are reported. Bulls are more likely to have interstitial cell tumors, but Sertoli cell tumors are reported.

The 3 main testicular neoplasms of dogs are the sex cord-stromal tumors (the Sertoli cell tumor and interstitial [endocrine] cell tumor) and the germ cell tumor (the seminoma). The fourth most common, but rare, is a mixed germ cell-gonadal stromal neoplasm. Multiple types of neoplasia may be found in one testis. Most primary testicular neoplasms in dogs are benign. Exceptions are rare, but malignant Sertoli cell tumors and seminomas are reported. Identification of metastasis in lymphatics, spermatic cord, lymph node, or distant sites is the only way to determine that the neoplasm is malignant; there are no good cytologic or histologic markers of malignancy.

Most neoplasms cause enlargement of the testis. In general, seminomas are white, soft, and bulge on cut section. Sertoli cell tumors induce fibrous tissue so they are white and tough. The interstitial cell tumor is yellow, soft, and often contains areas of hemorrhage. *Sertoli cell tumors, and rarely interstitial cell tumors, may produce a hyperestrogenism syndrome and feminization.* In dogs, this causes attractiveness to other male dogs, gynecomastia, and alopecia. Prostatomegaly and squamous metaplasia of the prostate also occur. Some animals will develop bone marrow suppression and poorly responsive pancytopenia. Preputial epithelial cytology changes so that more superficial epithelial cells are seen. Affected animals return to normal after removal of the neoplasm. Not all dogs will have a raised serum estrogen concentration. Inhibin secretion by the neoplastic Sertoli cells inhibits the secretion of FSH and LH by the pituitary, which in turn inhibits testosterone production and presumably alters the ratio of estrogen to testosterone. Feminization is much more common when the neoplasm is larger, and therefore is more common in cryptorchid dogs. It is also in these dogs that the unfortunate sequel of testicular torsion can occur.

Testicular tumors arise mostly in mature and old animals; the occurrence of interstitial cell tumors in dogs increases with increasing age. Canine testicular tumors are found more frequently in the right than in the left testis, and this is also true for cryptorchid testes.

Other neoplasms of the testis include the mixed germ cell–sex cord–stromal neoplasms, rete adenoma and adenocarcinoma, embryonal carcinoma, histiocytic sarcoma, leiomyoma, peripheral nerve sheath tumor, osteosarcoma, hemangioma, hemangiosarcoma, lymphangiosarcoma, and mast cell tumor.

Metastasis of neoplasms to the testis is rare. Lymphoma in the horse, dog, and bull, and hemangiosarcoma in the boar and dog are reported. The list will no doubt increase in length if pathologists routinely examine the testes at all autopsies.

Ectopic interstitial cell tumors are described in cats, and extratesticular Sertoli cell tumors occur in dogs. Epididymal neoplasms are exceedingly rare.

Sex cord–gonadal stromal tumors

Interstitial (Leydig) cell tumor. *Interstitial cell tumors have the phenotype of the interstitial endocrine cells.* They are grouped with Sertoli cell tumors in resembling tissue of the sex cords or stroma. Interstitial cell hyperplasia occurs periodically and there are varying opinions for when hyperplastic nodules become truly neoplastic, if they do. Some categorize these by

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size—either related to the size of the diameter of seminiferous tubules or in centimeters. Such a separation is artificial.

In the dog, interstitial cell tumors occur in older animals. They also occur in the bovine testis, in the older age groups, and mainly in Guernseys. There are very few reports of testicular neoplasia in boars, but interstitial endocrine cell hyperplasia and tumor are more common than others. In horses, the tumor develops almost exclusively in a cryptorchid testis. Cats develop interstitial cell tumors rarely; ectopic tumors are reported, especially in previously castrated animals.

Some interstitial cell tumors of dogs produce excess androgen, but *most tumors do not cause signs of hyperandrogenism*. Signs of hyperestrogenism were observed in a few dogs with interstitial cell tumors and estradiol concentration in testicular venous blood of affected dogs may be elevated. The condition is corrected by removal of the neoplasm. Multiple perianal hepatoid adenomas, tail gland hyperplasia, and prostatic enlargement may also be found.

Nodular hyperplasia may be a preneoplastic change in the dog. Hyperplastic nodules occur especially in testes that have undergone senile atrophy and, although they may be macroscopically visible, the nodules are small, nonencapsulated, and consist of an increased number of interstitial endocrine cells in the intertubular stroma. Hyperplastic cells are regular in form and size with increased acidophilia of the cytoplasm; mitoses are not seen.

Interstitial cell tumors in the **dog** are often multiple, but may be solitary and unilateral or bilateral (Fig. 5-40). Most are from 1 mm to 2 cm diameter; only exceptionally are they large enough to increase the size of the organ. They may make the organ irregular in contour with the rounded bulge of the tumor being visible in an otherwise small, soft, atrophic testis. On cut surface, the tumors are well demarcated, spheroidal, and yellow. They are prone to hemorrhage, which causes dark discoloration and cyst formation. Large tumors are often multinodular. The consistency is soft, there being little stroma, and the cut surface is slightly greasy.

Interstitial cell tumors grow slowly and expansively with surrounding compression atrophy. They are not notably invasive. In bulls with interstitial cell tumors, semen production and fertility may be reduced.

The cells in the dog are well differentiated interstitial endocrine cells, being round or polyhedral, with abundant cytoplasm that may be granular or vacuolar and that often contains yellow or brown lipochrome pigment (Fig. 5-41). The neoplastic cells in the bull are not vacuolated and contain very little lipid. Sometimes and in some tumors the cells have a more mesenchymal appearance, being spindle-shaped with an indistinct cytoplasmic outline and a streaming arrangement. It is in such tumors especially that necrosis and cyst formation occur. The nuclei are regular in size and stain affinity, and mitoses are rare. The stroma is scant, and vessels may resemble sinusoids, as occurs in endocrine organs.

Intranuclear cytoplasmic invaginations or inclusions occur in up to 15% of neoplastic cells in canine interstitial cell tumors. The inclusions, which are strongly PAS-positive and composed of smooth and rough endoplasmic reticulum, vesicles and lipid vacuoles, myelin figures, and disrupted membranous profiles, were not found in other testicular tumors. Nuclei containing these invaginations are larger. Except where invaginations are present, the ultrastructural appearances of neoplastic and normal interstitial endocrine cells in the dog are similar.

Immunohistochemistry of canine interstitial cell tumors is usually not required because the histologic findings are characteristic. A variety of antibodies were used on interstitial cell tumors and GATA4 appears to be consistently positive.

A high incidence of telangiectasis of the liver, thyroid C (parafollicular) cell tumors, and infertility was observed in Guernsey **bulls** with interstitial cell tumors, but a cause and effect was not proven.

Interstitial cell tumors in **stallions** occur most often in undescended testes. They contain 2 cell types; the first is essentially a hypertrophic interstitial endocrine cell but the other is a pleomorphic fusiform cell with fibrillar, vacuolated cytoplasm and indistinct borders. Increased hormone

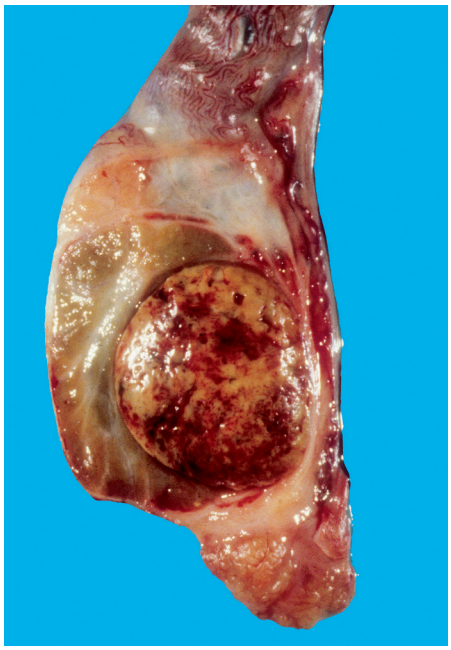

Figure 5-40 Intratesticular **interstitial cell tumor** in a dog. These are soft and tan, with regions of hemorrhage. The adjacent testis is atrophic.

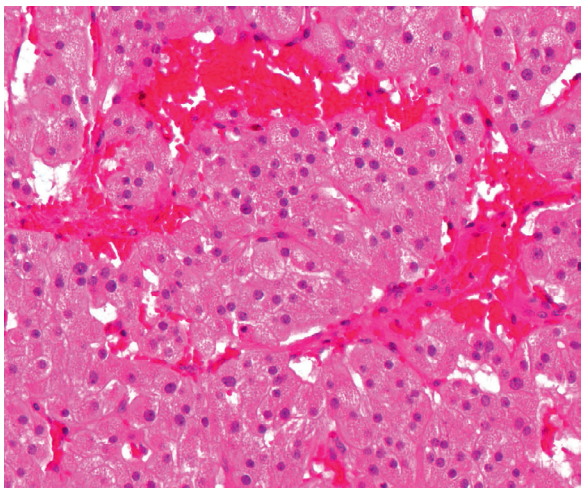

Figure 5-41 Microscopic appearance of an **interstitial cell tumor** in a dog. Neoplastic cells are in an endocrine pattern, with large polygonal cells packeted into groups by a vascular fine fibrous stroma.

concentration is reported in horses with these tumors, and viciousness corrected by castration was observed.

Extratesticular interstitial cell tumors are reported in **cats** and rarely in dogs. In cats, they are found in the scrotal skin and spermatic cord of previously neutered males, some of which develop male behaviors of spraying and male odors. Deposition of interstitial endocrine cells in the peritesticular tissues at the time of castration is believed to be the initiating event—continuous stimulation of the cells by LH results in hyperplasia and subsequently neoplasia. Epididymal interstitial cell tumors in tomcats arising from ectopic tissue are reported.

Interstitial cell tumors in other species, including camelids, are very rare.

Sertoli cell tumor. *The Sertoli cell tumor is common in dogs but rare in other domestic species.* It is reported in the bull, stallion, ram, and tomcat. They cause enlargement of the affected testis, some animals develop a hyperestrogenism syndrome, and metastasis is rare.

Feminization is part of a *hyperestrogenism syndrome* that includes squamous metaplasia of prostate and suppression of bone marrow. Not all dogs with feminization or other components of that syndrome have a higher concentration of serum estrogen. When present, the syndrome is from excess estrogen or excess inhibin secretion reducing testosterone concentration. Larger tumors are responsible for the hyperestrogenism syndrome, so the mass of the tumor is correlated with the quantity of hormone elaborated. Poorly differentiated tumors may not produce hormones, regardless of size.

In the hyperestrogenism syndrome, attractiveness to other male dogs is well known. Other changes include reduction of libido, female distribution of body fat, cutaneous and pilosebaceous atrophy leading to symmetrical alopecia and hyperpigmentation, atrophy of testes and penis, an estrogenic form of mammary development, swelling of the prepuce, and hyperplasia or squamous metaplasia of the prostate. Enlargement of the seminal colliculus with partial obstruction of the urethral lumen may also accompany prostatic changes in these dogs.

Some dogs develop *depression of myelopoiesis* with resultant thrombocytopenia and hemorrhage, anemia caused by blood loss and/or reduced erythropoiesis, and infection and fever with neutropenia. Recovery may follow castration and supportive therapy.

Metastasis of Sertoli cell tumor, although rare, is often into the spermatic cord. Obstruction of the testicular vein and lymphatics may result in hydrocele with massive swelling of the scrotum. Metastasis to the regional lymph node and beyond is unusual.

The macroscopic appearance of a Sertoli cell tumor is distinctive. They are usually either solid or cystic, and the larger tumors are multinodular, lobulated and enclosed in a tense testicular capsule (Fig. 5-42; see also Fig. 5-19). The cut surface usually is white and tough. *The firmness of the tumor is due to the abundance of its fibrous stroma*, something the other two common testicular tumors have in small amounts only.

Histologically, Sertoli cell tumors begin within seminiferous tubules and progress with penetration of the basement membrane and finally to the formation of a macroscopically visible mass. It is unusual to see hyperplastic or preneoplastic microscopic foci in normal testes. Stroma is always plentiful, and it may be dense collagen (Fig. 5-43A). The stromal tissues

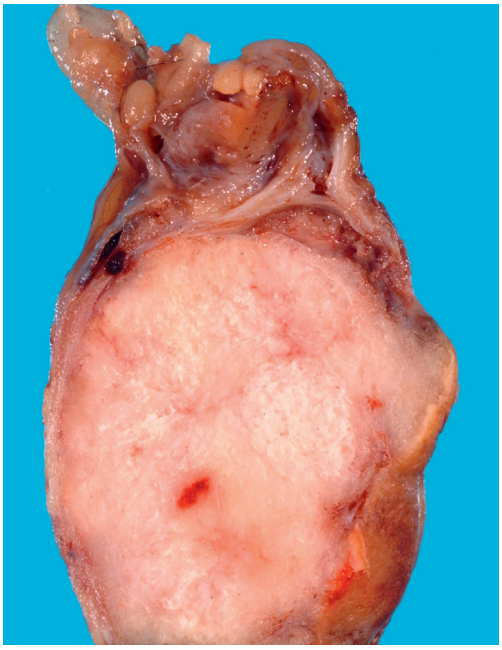

Figure 5-42 **Sertoli cell tumor** in a dog. These are white, tough and often have fine septa of fibrous tissue visible.

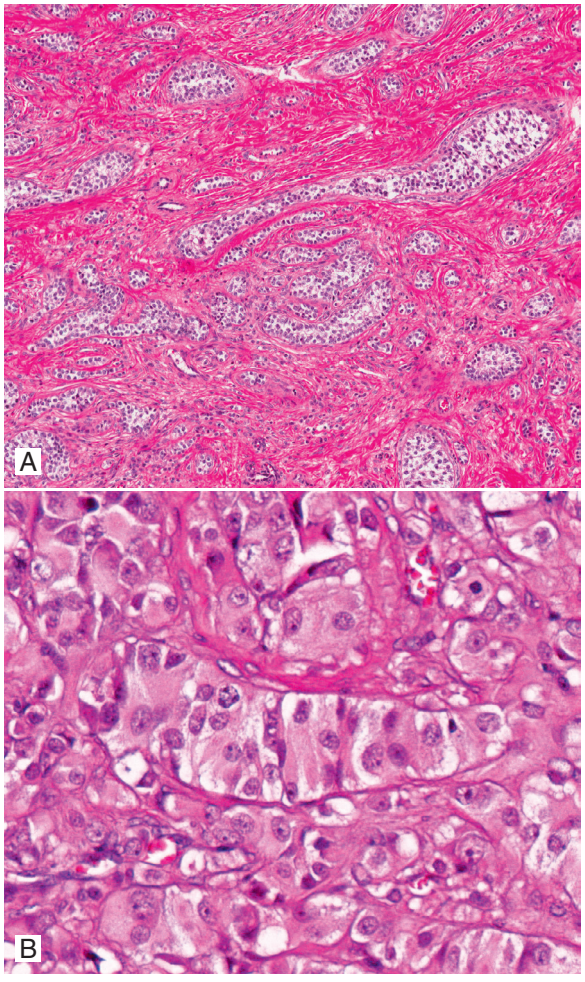

Figure 5-43 **A.** Histologic appearance of **Sertoli cell tumor** in a dog showing tubular structures separated by abundant fibrous tissue. **B.** On higher magnification, the cells tend to bridge from one side of the tubular structure to the other.

contribute to a tubular pattern, and the neoplastic cells tend to palisade. In smaller tubules they stretch from one side of the tubule to the other (Fig. 5-43B). Some form cystic structures that may be confused with carcinoma. In the well-differentiated tumors, the cells resemble normal Sertoli cells, being elongate with foamy acidophilic cytoplasm and small, basally located, nuclei. In less differentiated varieties, the cells are still elongate, have eosinophilic cytoplasm, but the nuclei are oval and pleomorphic, and are no longer basally located against the trabecular pole. In the less common form of the tumor, the cells show little or no tendency to palisade but are discrete and spherical with well-defined eosinophilic cytoplasm and anisokaryosis. Mitoses are sparse in most. Lipids are demonstrable in the neoplastic cells as large droplets and globules in more differentiated tumors, and as fine droplets in the least differentiated tumors. There is little correlation between histologic type and metastasis.

It is not possible to generalize about the detailed immunohistochemical staining characteristics of Sertoli cell tumors because of variable results. Neoplastic cells should be positive for vimentin (as are interstitial endocrine cells) and negative for cytokeratin stains (but not always). There are varied reports of staining for many different antigens including S100, melan A, GATA4, inhibin, and anti-Müllerian hormone (AMH) to name a few. If inhibin and AMH staining are present, a diagnosis is made with greater confidence.

Canine Sertoli cell tumors have characteristic electron microscopic structures including intercellular junctions and crystals of Charcot-Bottcher. If these are not visible, Sertoli cell tumors have abundant organelles that allow differentiation from interstitial cell tumors and seminomas.

Extratesticular Sertoli cell tumors occur in dogs. They are located in the prescrotal and scrotal region or spermatic cord of neutered dogs. They presumably develop from remnants implanted at castration. Prolonged stimulation of testicular remnants eventually allows transition from hyperplasia to neoplasia. The tumors are identical to Sertoli cell tumors within the testis, and some produce a hyperestrogenism syndrome. No metastases are documented.

In general, the gross and microscopic appearance of Sertoli cell tumors in the **bull** resembles those in the dog. Early age of slaughter of most food animals precludes studies on true tumor occurrence with increasing age. In one study in which bulls and buffaloes were kept until 9-14 years for draft purposes, 20 of 161 testes examined contained neoplasms; all but one were Sertoli cell tumors. Seven tumors were in undescended testes. In contrast to dogs, bovine Sertoli cell tumors are often in newborn or young calves, suggesting altered embryogenesis. They sometimes have laminated intratubular concretions resembling those seen in bovine testicular hypoplasia and cryptorchidism. A simultaneous occurrence of Sertoli cell tumor and epididymal aplasia was observed. One bovine Sertoli cell tumor was in a testis of an animal in which castration by the burdizzo method was attempted 5 years previously. Metastasis of Sertoli cell tumor to the pampiniform plexus is reported in a bull; there is no clear evidence of a hyperestrogenism syndrome.

One case of Sertoli cell tumor in a **stallion** involved the single descended testis; a ductal pattern of neoplastic Sertoli cells, which contained clusters of distinct hyaline bodies, was evident.

Sertoli cell tumors in the **ram** are comparable to those in the bull. Hyperplastic Sertoli cells occur in cryptorchid rams (see Fig. 5-17), but their potential to develop into neoplasms seems unlikely, given the rarity of the tumors.

Sertoli cell tumors in other species, including camelids, are very rare.

Germ cell tumors

Seminomas. Seminomas are common in canine testes and are reported in the bull, boar, stallion and mule, ram, buck, tomcat, and bull camelids. They occur in *older animals* and are disproportionately common in cryptorchid testes. Their phenotype is usually spermatocytic, and there is subclassification into classical and spermatocytic types based on periodic acid Schiff (PAS) and placental alkaline phosphatase (PLAP) staining. Classical seminoma is positive for both. Although a solitary tumor is observed macroscopically, they are histologically multifocal in the affected testes. These tumors typically do not produce hormones; if there is evidence of a hyperestrogenism syndrome, other possibilities must be completely excluded. They are usually benign, but metastatic examples are reported. There are no known factors to predict the metastatic potential of seminomas.

The main presenting sign is testicular enlargement. Sudden enlargement of the testis and pain caused by hemorrhage and necrosis in the tumor, can occur. In all species, the cut surface is coarsely lobulated by a few fine trabeculae. The color is usually white or gray-white, except in stallions in which they are often tan (Fig. 5-44), and the texture is soft; they usually bulge from the cut testicular surface (see Fig. 5-44). If lightly squeezed, a milky fluid may exude from them. The texture and color closely resemble that of neoplastic lymphoid tissue.

Microscopically, intratubular and diffuse types are recognized. The earliest development of the tumor is intratubular and even in some large examples, intratubular growth is still evident elsewhere (Fig. 5-45A). Rupture of the tubules soon occurs and the growth becomes confluent, forming broad sheets of closely packed cells with scant supporting stroma. The cells are large and round or polyhedral, with a rim of visible cytoplasm that may be basophilic or eosinophilic (Fig. 5-45B). The nuclei are large, round, and hyperchromatic, with one or more large acidophilic nucleoli. In some tumors, the nuclei are larger and vesicular but still regular in shape. In many seminomas, it is possible to find scattered mono- or multinucleated giant cells with abundant granular acidophilic cytoplasm. A useful distinguishing feature is the presence of focal nodules of, or diffuse, CD8+ lymphocytes. Whereas degeneration of tubules at the edge of the tumor is normally

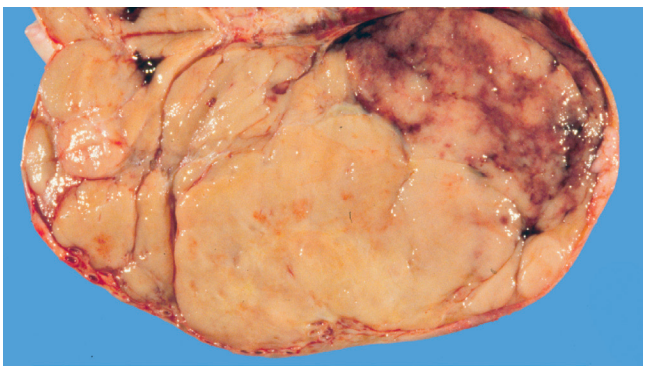

Figure 5-44 Multinodular and yellow tan appearance of a **seminoma** in a horse. In other species, the neoplastic tissue varies from white to tan and is friable.

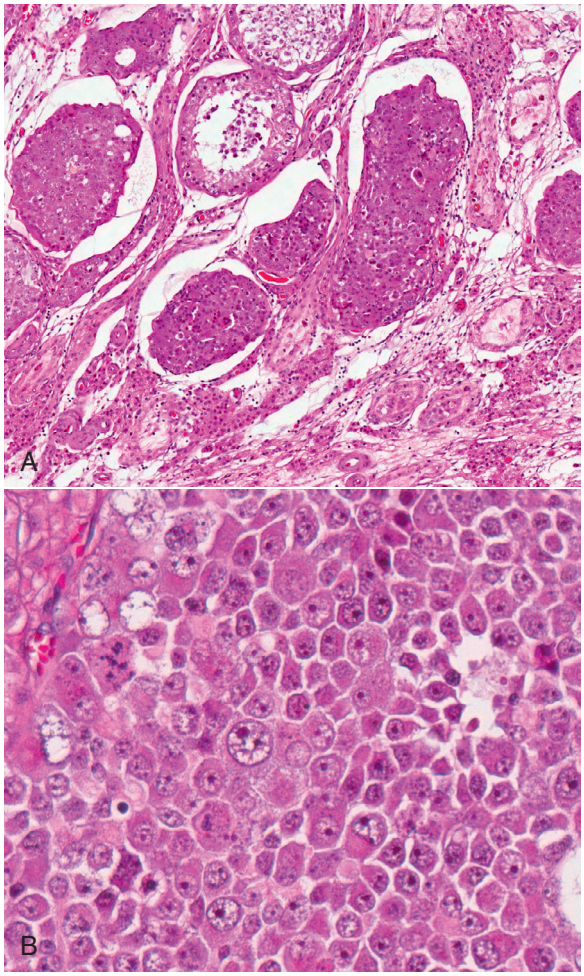

Figure 5-45 **Seminomas** usually have a combination of intratubular (**A**) and diffuse growth. The adjacent testis may be degenerate, as was the case in this dog. **B.** Histologically, the cells are large round cells with scant cytoplasm and large nuclei with prominent nucleoli. Mitoses are frequent.

evident, occasional foci of intratubular germ cells and intratubular seminoma is seen.

Ultrastructurally, neoplastic cells resemble normal germinal epithelium and have oval nuclei, straight cell borders, a distinct Golgi complex, and a scarcity of cytoplasmic organelles. Intercellular bridges, as seen in normal germinal cells, are present in seminomas. In all cases the cells are distinct from cells of interstitial or Sertoli cell tumors.

Germ cells stain by immunohistochemistry using antibodies including calretinin, KIT, PGP 9.5, E cadherin, GATA4, inhibin alpha, and NSE, but no staining pattern differentiates them from other testicular tumors except GATA4 staining because germ cells are negative but the majority of Sertoli cell and interstitial cell tumors are positive.

In the **stallion**, seminomas occur in older animals and often in cryptorchid testes. They can weigh up to 9 kg, and some are metastatic with spread to most parts of the abdominal cavity and occasionally to the thoracic cavity.

Intratubular seminomas are reported in mature and aged **rams** that have concurrent testicular degeneration. The proliferating cells are multifocal within seminiferous tubules and do not attain sufficient size to be recognized grossly. Rarely a malignant form of seminoma occurs in the ram, producing overall enlargement of the testis, hemorrhage, necrosis, and obliteration of the entire testis.

Seminomas are exceedingly rare in other species.

Teratoma. *Teratoma of the testis is found periodically in foals, but is rare in other domesticated mammals.* It occurs in cryptorchid equine testes, but whether it forms preferentially in retained testes or it prevents normal descent is not known. There is a report of testicular teratoma that caused partial obstruction of the colon in a neonatal foal.

Macroscopically, teratomas are single or multiple and vary in color and texture. They are usually <10 cm in diameter but may be >25 cm. A cystic and/or multilocular structure is common and hair and mucoid or sebaceous secretions are seen, hence frequent use of the term *dermoid cyst*. Yellow-white solid masses with fibrous, adipose, cartilaginous, and bony tissue are also frequent.

Histologically, *structures from all embryonic germ layers may be present*, including ectodermal (dermoid cysts, hair, teeth), neuroectodermal (nervous tissue, melanoblasts), endodermal (salivary gland, respiratory), or mesodermal (fibrous or adipose tissue, bone, muscle). Nervous tissue is almost always present, and adipose tissue is also very common. Testicular tissue adjacent to a teratoma may have reduced spermatogenesis, with various degrees of tubular degeneration. Gonadal teratoma is further discussed in Vol. 3, Female genital system.

Embryonal carcinoma. *Embryonal carcinoma is exceedingly rare in animals* but it is a well-known malignant testicular neoplasm of humans. The cells are of indifferent embryonic types, thus it is similar to teratoma but much more primitive. Trophoblastic differentiation and demonstrable α-fetoprotein in the epithelial cells supports the diagnosis.

Teratocarcinoma, a neoplasm with features of teratoma and embryonal carcinoma, is reported in the horse.

Mixed germ cell–sex cord stromal tumor

These neoplasms, the fourth most common primary testicular tumor in the dog, are a combination of germ cells (seminoma) and sex cord stromal cells (interstitial endocrine cells and Sertoli cells). Cell types are found together and are different to when a Sertoli cell tumor collides with a seminoma. *Gonadoblastoma* is a synonym. These are likely underreported. The lesions grossly resemble Sertoli cell tumors because they are firm, white to tan, and expansile. Larger neoplasms may be hemorrhagic. *Histologically, they are a combination of seminoma and Sertoli cell tumor, with the tubular structures of Sertoli cell tumors containing germ cells.* Immunohistochemical staining helps confirm the dual nature of this neoplasm.

Mixed germ cell–sex cord stromal tumors are also reported in stallions.

Other primary tumors

Adenomas and adenocarcinomas presumably originating from the rete testis are described in horses and dogs. These have tubulopapillary structures with scant supporting stroma. The papillae and anastomosing tubules are lined by small closely packed cells with scant cytoplasm either in single or multiple layers. Evidence of transformation from normal to neoplastic rete epithelium is a useful criterion for diagnosis. Exclusion of teratoma by taking multiple sections, or of it being a distant metastasis, is also required. Immunohistochemically, they will stain with antibody to cytokeratin.

Reports of *mesenchymal tumors* of the testis are mostly individual cases. They include leiomyoma and leiomyosarcoma, hemangioma, hemangiosarcoma, lymphangioma, and peripheral nerve sheath tumor. Mast cell tumor and histiocytic sarcoma are also reported.

Neoplasia of the epididymis is a very rare event. Any tissue may transform, and carcinoma is reported. Metastases from elsewhere occur too, and lymphoma may occur. Interstitial cell tumor of the epididymis of the cat is a recognized disease and arises from ectopic interstitial endocrine cells.

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Miscellaneous diseases of the testis and epididymis

Spermatic granulomas occur at any location. The most recognized syndrome is *spermatic granuloma of the epididymal head*, a condition resulting from blind-ending efferent ductules. It occurs in virtually every species; it is not reported yet in the cat.

Adenomyosis of the mesonephric ducts is a histologic finding in which *diverticula of the epithelium of the epididymis or deferent duct protrude through the muscular wall*. Spermatozoa may become entrapped and incite an inflammatory reaction. Hyperestrogenism may be an inciting cause. Adenomyosis is the suspected underlying defect when a sperm granuloma is found in a location apart from where blind-ending efferent ductules would be expected. Virtually every species develops adenomyosis of the mesonephric duct.

The **rete testis** is a series of interconnected channels that join the seminiferous tubules to the efferent ductules. It has intratesticular and extratesticular segments. Spermatophagia occurs in this area, and immune reactions to spermatozoa may be manifested by inflammation. There are 2 main primary diseases of the rete: *neoplasia and cyst formation*. The epithelial cells are the origin of adenomas and adenocarcinomas in horses, dogs, and other species. Cysts of this region occur in the stallion, dogs, and cats. Secondary dilation of the rete testis occurs with obstruction of the efferent ductules or epididymis.

SPERMATIC CORD

The spermatic cord is composed of the 3 arteries, veins, lymphatics, 3 nerves, and deferent duct. It is covered by 3 layers, including the cremaster muscle and fascias. These are critical structures for the function of the testis and epididymis. Scrotal hernia and varices of the pampiniform plexus are the most commonly recognized diseases of the spermatic cord. Most of the other diseases become differential diagnoses for these.

Varicocele

A varicocele is a dilation and tortuosity of the veins of the pampiniform plexus. Varices of the spermatic veins are most common in old rams (Fig. 5-46). They occur sporadically in others, such as the bull, stallion, and dog, as an incidental finding or secondarily to conditions in which there is constriction of the veins of the spermatic cord. Experimental induction is achieved by generating partial obstruction of the left renal vein.

Varices are seldom recognized unless they are thrombosed. There is no concrete evidence that small varicoceles are detrimental. Large ones are, because of their size and the reduced ability of the animal to raise the testis to maintain thermoregulation, or because of alteration of blood flow and changed testicular oxidant/antioxidant balance. The pathogenesis of varicocele is poorly understood. In humans, the left unilateral location is the result of altered hemodynamics from insertion of the testicular vein to the renal vein rather than directly to the vena cava. Evidence in humans with varicose veins of the legs suggests that the elastic properties of the walls of the veins, arterial flow, and valves in veins are major factors. It is difficult to implicate intimal sclerosis of the spermatic vessels as older animals of all species develop this, but so few develop varicocele.

Varicoceles appear as dark red, up to 3-cm diameter, nodules enclosed in fascia of the spermatic cord proximal to the testis. Varicoceles may have large organizing laminated thrombi, typical of venous thrombi. *Differential diagnoses* of varicocele include neoplasia (mesothelioma), scrotal hernia, scrotal lymphadenitis, spermatic granuloma of the epididymal

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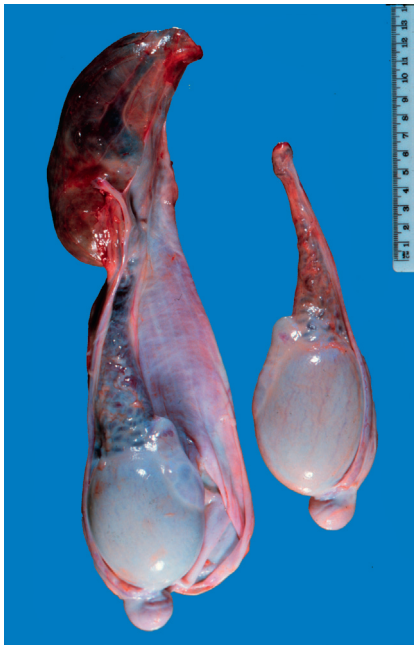

Figure 5-46 Varicocele with thrombosis in a ram. The grossly dilated and thrombosed pampiniform plexus causes a large multilobular mass above the testis in the spermatic cord.

head or deferent duct, and cystic retained mesonephric or paramesonephric ducts.

Varicocele is most common in the **ram**, where it is bilateral, or unilateral with no apparent predisposition as to side. Large varicoceles are always thrombosed and there is overt testicular degeneration, occasional thrombosis of testicular vessels, and reduced testis:body weight ratios.

Other vascular lesions

Intimal sclerosis of testicular veins is common in older males, and described in rams and bucks. The arterial changes, which tend to be bilateral, consist of fibroplasia of the intima. Intimal and/or medial mineralization also occurs in branches of the testicular artery.

Vasculitis of testicular, deferential, and cremaster arteries may be found in malignant catarrhal fever and bovine viral diarrhea virus infection of bulls. Dogs, particularly Beagles with canine juvenile systemic vasculitis, and occasionally in other vasculitides, have involvement of these vessels. Apparent *hypoplasia* of veins of the spermatic cord is reported in bulls with thickening and degeneration of the testicular artery.

Although studies in the bull have not demonstrated a direct connection between venous and arterial blood vessels of the pampiniform plexus, *functional arteriovenous anastomoses* through small vessels do occur in normal bulls, boars, and rams, and may represent a further means of thermoregulation of the testis. A large anastomosis of the spermatic artery and vein is reported in a stallion with an abdominal testis.

Scrotal hernia

Inguinal hernia occurs when abdominal contents bulge into the inguinal canal. *Scrotal hernia* occurs when abdominal contents are within the space between the vaginal tunics (the vaginal sac). It occurs in all species as either congenital or acquired disease. A genetic cause is either proven or suspected. Scrotal hernias develop if there is failure of closure of the internal inguinal ring, incomplete obliteration of the vaginal process, weakness of the triangle of the inguinal region, an abnormality in smooth muscle in the wall of the hernia, or increased intra-abdominal pressure.

In **boars**, 3 or 4 candidate genes are linked to scrotal hernia. There is a possible link with genes involved with cryptorchidism. In **stallions**, the disorder is either congenital and often resolves by 3-6 months of age, or it is acquired and is potentially life threatening because of intestinal strangulation. In the *congenital form*, a portion of the jejunum enters the vaginal sac; rupture of the vaginal tunics at birth may result in the loop of intestine lying in a subcutaneous location. In the *acquired form* in entire animals, exercise or some activity such as serving a mare may precede development. Left- and right-sided hernias occur with equal frequency. Herniation of the intestine usually obstructs vascular supply to the testis, necessitating castration at the time of surgical repair. The acquired form is very rare in geldings.

Miscellaneous diseases of the spermatic cord

Other lesions of the spermatic cord may involve the deferent duct, blood vessels, nerves, lymphatics, cremaster muscle, or tunics. Some of these diseases, particularly disorders of sexual development, are described elsewhere in more detail.

Inflammation of the spermatic cord is **funiculitis**; it follows open castration. Pigs and other species where environmental bacterial contamination is high develop necrotic funiculitis. Ascending infection with subsequent diffuse peritonitis, and tetanus, are common complications. "*Scirrhous cord*" is the condition when there is an open draining scrotal wound, abscessation, and granulation of the cord. The prevalent form occurs in steers and geldings. The classical scirrhous cord of geldings is a pyogenic infection, usually by staphylococci, which produces the pyogranulomatous inflammation commonly called *botryomycosis*. *Brucella canis* can cause funiculitis in infected dogs. Funiculitis occurs in cats that have hair trapped at the site of severance of the cord at castration. It accompanies reactions to, or infection of, suture material at castration.

Neoplasms arise in these structures, or are metastases from other locations. The range of neoplasms is similar to those of the scrotum and testis (listed earlier). Primary neoplasms of any of the structures can occur, including fibrous tissue, skeletal and smooth muscle, endothelium, or mesothelium. Neutered dogs and cats can develop extratesticular Sertoli and interstitial cell tumors of the spermatic cord.

Verminous granulomas caused by migrating larvae of *Strongylus* spp. occur in the spermatic cord and testes of horses.

Spermatic granuloma of the deferent duct is a sequel to vasectomy, and is occasionally seen as spontaneous disease.

Ectopic adrenal tissue is occasionally found in the spermatic cord, often near the efferent ductules or head of the epididymis. Ectopic splenic tissue can also be found here.

Disease of the *scrotal lymph node* can be confused with disease of the spermatic cord. Caseous lymphadenitis in sheep and lymphoma in dogs are 2 common diseases that may cause enlargement of the node and be mistaken for varicocele, hernia, or other abnormality. Lymph and therefore inflammatory infiltrates, spermatozoa, and metastases from intrascrotal neoplasia can drain to the superficial inguinal, or lateral and medial iliac nodes.

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ACCESSORY GENITAL GLANDS

Vesicular glands and ampullae

Disorders of sexual development

An important disorder of sexual development affecting the vesicular glands (seminal vesicles) and ampullae of the deferent ducts is **segmental aplasia of the mesonephric duct.** This has been studied in the bull, in which it appears to be heritable. Aplasia or hypoplasia of this duct can be complete and thus the deferent duct and epididymis may also be affected, but usually only a segment is missing and it is usually the epididymal tail that is missing. Aplasia is mostly unilateral and the ampulla on the affected side is completely absent or rudimentary and the vesicular gland is markedly hypoplastic and sometimes cystic. *Vesicular gland hypoplasia* of variable severity may occur independently of aplasia of the ampullae or deferent duct. The vesicular glands on the side of hypoplastic testes are usually smaller than normal.

Other disorders of development of the vesicular glands and ampullae of the bull include *fusion* of the vesicular glands and appendages of the ampullae. There is variation in the *anatomic relationship* of ampullae to the vesicular glands in normal bulls; the ampullae are entirely dorsal to the vesicular glands in 40% of bulls, are entirely ventral in 40% of bulls, and in the remaining 20% of animals are intermediate. These disorders of development and anatomic variations are identified at rectal examination. Anomalous glands are predisposed to inflammation, may affect the freezability of semen, but are unrelated to fertility in natural breeding systems.

Cystic dilation of the lumina of occasional lobules, or a general dilation of ducts in one, and sometimes both, vesicular glands, occurs in bulls, horses, and swine.

Inflammation of the vesicular glands

Vesicular adenitis, often with inflammation in ampullae, is a common lesion in the bull (Fig. 5-47), and is rare in the stallion and boar. Macroscopically apparent vesicular adenitis and or ampullitis is rare in the ram, but histologic lesions are frequent in animals infected with *Brucella ovis, Actinobacillus seminis,* and *Histophilus somni* (Fig. 5-48), particularly if they have epididymitis caused by these organisms. Vesicular adenitis in bulls is detected on rectal palpation, and by the presence of neutrophils or pus in semen. Young bulls, less than 2 years of age, are frequently affected.

Two general forms of vesicular adenitis occur in the **bull**. There is a *degenerative or necrotic form* in which there is a slight increase in size and consistency, and a *chronic interstitial form*

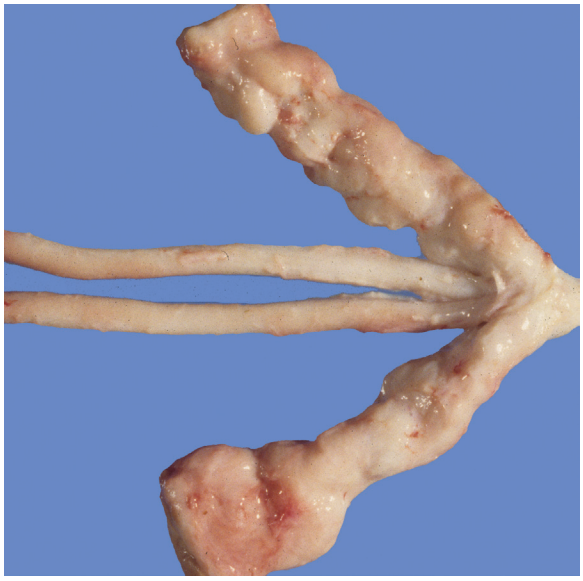

Figure 5-47 **Chronic vesicular adenitis** in this bull caused fibrosis, loss of lobulation, and shrinkage of the glands.

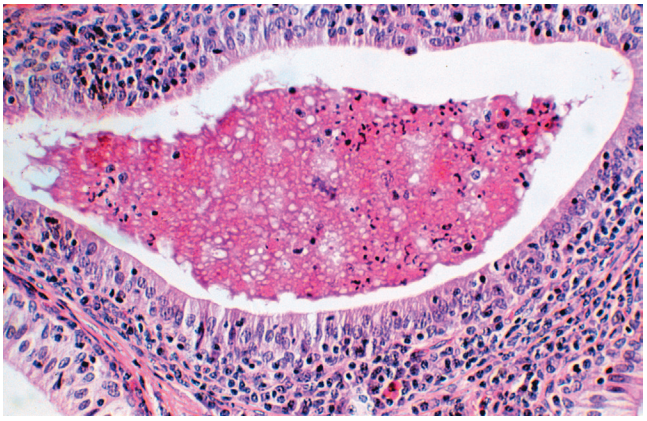

Figure 5-48 Microscopically visible **vesicular adenitis** in a ram with *Brucella ovis* infection. Large numbers of lymphocytes and plasma cells are in the interstitium. The glands contain debris.

(see Fig. 5-47) where the glands are increased in size and are firm and lack lobulation from fibrosis. In the degenerative form, neutrophils, sloughed epithelium and cellular debris, and intensely basophilic material fill acini. The chronic interstitial form is dominated by fibrosis and many lymphocytes, plasma cells, histiocytes, neutrophils, and occasional eosinophils within the stroma. The epithelium usually is normal but may be metaplastic in some areas. Acini contain a small amount of finely granular eosinophilic material, occasional neutrophils, and desquamated epithelium.

Numerous *infectious agents* are isolated from bovine vesicular adenitis, but the precise roles of most have yet to be determined. In chronic vesicular adenitis, bacteriologic investigations are often negative. *Trueperella pyogenes* is the most common isolate. Large abscesses may be present also and these may involve adjacent tissue, and adhesions and fistulas form with the rectum or bladder. Staphylococci and streptococci generally do not form large abscesses, but more often small focal or diffuse suppurative inflammation. Vesicular adenitis caused by *Brucella abortus* is fibrinopurulent, progressing to necrosis, suppuration, and dystrophic mineralization;

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granuloma formation is rarely observed. Tuberculous vesicular adenitis causes an increased size of vesicular glands with characteristic caseation and granulomas.

Several viruses, including the virus of infectious bovine rhinotracheitis-infectious pustular vulvovaginitis (bovine herpesvirus 1), may infect the accessory genital glands of the bull. Clinical signs of vesicular adenitis in such cases are reported to be mild and transitory. The vesicular glands and prostate are the most productive sites for viral replication in bovine viral diarrhea virus infection in bulls, but neither gross nor microscopic lesions are observed. *Mycoplasma bovis*, *Mycoplasma bovigenitalium*, and ureaplasmas were isolated from bulls with vesicular adenitis, and unequivocal lesions have resulted from experimental infection. Apart from variable numbers of eosinophils in these lesions, they are nonspecific. *Mycoplasma bovigenitalium*, however, was isolated from vesicular gland secretions from a large proportion of normal pubescent bulls. As with the mycoplasmas, *Chlamydophila* spp. are isolated from the semen and epididymides of bulls, and their possible role in vesicular adenitis is unknown. The vesicular glands may also be an important site for localization of *Leptospira* spp. *Leptospira interrogans* serovar *hardjo* was isolated with equal frequency from vesicular glands and kidneys of naturally infected bulls, thereby suggesting the possibility of venereal transmission.

The *pathogenesis* of bovine vesicular adenitis is unresolved. Hematogenous infection of the glands seems probable in some cases, but ascending infection from the urethra is probable. Stress, reflux of urine or semen into the vesicular glands, and congenital defects in the mesonephric duct system predispose to infection.

In **pigs, sheep,** and **goats,** vesicular adenitis is of less importance than in the bull. It occurs in brucellosis caused by *Brucella suis*, *Brucella ovis,* and *Brucella melitensis*, respectively. The characteristic lesion is chronic, and resembles the chronic interstitial form seen in the bull (see Fig. 5-48). In boars, abscessation of the vesicular glands and prostate may accompany orchitis caused by *Burkholderia pseudomallei*. Abscesses in the vesicular glands of barrows may be the result of infection at the time of castration.

In the **stallion,** purulent, abscessating vesicular adenitis is described, but appears to be uncommon. Virus is shed for months in the semen of stallions infected experimentally with equine arteritis virus. The ampullae and bulbourethral glands are predilection sites. It is unclear whether there are lesions in infected tissues, or associated spermatozoal abnormalities. Bacterial vesicular adenitis and ampullitis occur sporadically and may be a cause of "colic."

Prostate and bulbourethral glands

The prostate and bulbourethral glands arise from endodermal epithelial buds from the middle or pelvic part of the urogenital sinus. Their responses to injury are similar. In bulls and rams, a local secretory IgA-based immune system develops here.

Disorders of sexual development

Disorders of development of the bulbourethral gland include *congenital retention cysts* in bulls, rams, and cats, and *aplasia, hypoplasia, and fusion* in bulls. *Melanosis* of the bulbourethral glands has been observed in the bull and boar.

Malformations of the prostate are infrequent and occur with disorders of development of the remaining genitalia including cryptorchidism. A prostatic appendage is reported in the bull where a polyp-like protrusion of prostatic tissue bulged into the urethral lumen. Congenital retention cysts occur in the bull and a cryptorchid boar. In some dogs, the dorsal median groove of the prostate may be indistinct so the bilobed structure is not evident.

Prostatic cysts and pseudocysts in the dog may be congenital or secondary to hyperplasia, neoplasia, or inflammation (see later). Cysts within the prostate may be *multiple cysts in prostatic hyperplasia, retention cysts, and cysts with squamous metaplasia*. Those outside the prostate are called paraprostatic cysts or pseudocysts (Fig. 5-49). Those lined by epithelium are true cysts (Fig. 5-50) and those without epithelium are pseudocysts. The precise origin of paraprostatic cysts is not clear. Most cysts attach to the prostate at a small localized area. The cysts are up to 30 cm long and 14 cm in diameter, and have a wall of compressed collagen and even bone (see Fig. 5-50). Fibrin may be present on the inner aspect of the larger cysts, as well as polypoid bony extensions into the lumen. Cysts become infected to form a prostatic abscess, although most

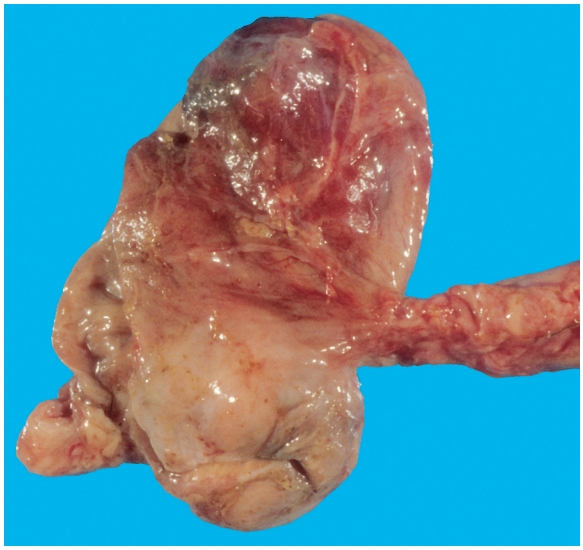

Figure 5-49 **Paraprostatic cyst** (upper) distorting the contour of the prostate (lower) in a dog. The bladder is to the right.

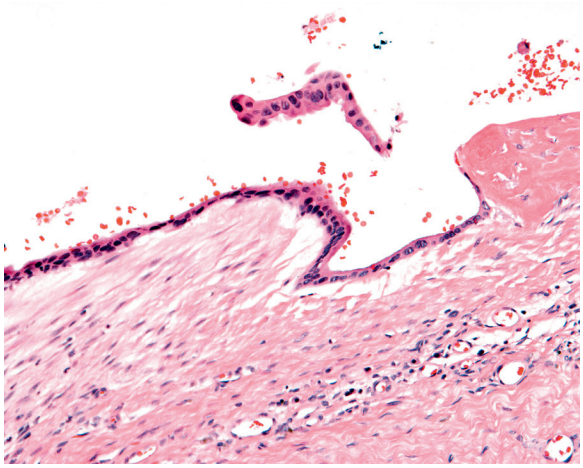

Figure 5-50 Microscopic appearance of **paraprostatic cyst** with epithelial lining, underlying fibrous tissue, and osseous metaplasia (right).

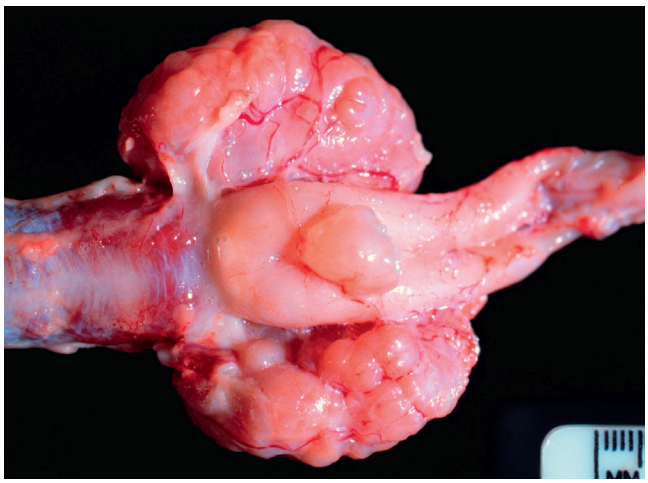

Figure 5-51 Cystic uterus masculinus (center) overlies the ampullae of this ram.

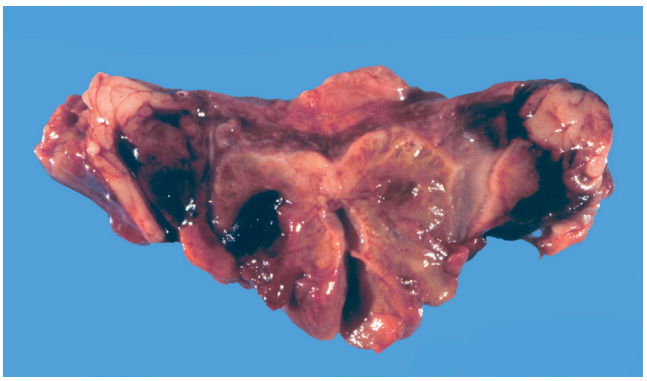

Figure 5-52 Transverse section of a canine prostate with **acute prostatitis**. Hemorrhage and edema involve the prostate and the periprostatic tissues.

have a sterile content and are devoid of pus, urine, and spermatozoa. *Hyperplastic prostatic and paraprostatic cysts* are partially lined by prostatic epithelium, and probably arise as outpouching of prostatic glandular epithelium through the discontinuous muscle coat of the gland. Cysts that are centrally located on the dorsal surface of the prostate may have arisen from vestiges of the paramesonephric duct, and form a uterus masculinus. *Uterus masculinus* occurs in males of most species, and they are in the connective tissue between the ampullae or deferent ducts (Fig. 5-51).

A true *cystic uterus masculinus* is lined by stroma and simple columnar epithelium that resembles endometrium. A cystic uterus masculinus occurs in old dogs and appears to be stimulated by estrogen, as occurs in Sertoli cell tumor. These may cause constipation, dysuria, or anuria. *Paraprostatic lymphatic cysts* are reported. They have no epithelial lining, are multilobular, and may have an endothelial lining. About 18% of paraprostatic cysts have a fluid content that is high in creatinine indicating it is urine. They are called *paraprostatic urinary retention cysts*. These may begin as hyperplastic prostatic cysts and thus communicate readily with the urethra. *Serosal inclusion cysts* and *hematomas* are other possibilities. For most, the lack of any characteristic feature makes determining their origin impossible.

Inflammation of the prostate and bulbourethral gland

Inflammation of the bulbourethral gland in the bull often accompanies vesicular adenitis. The cause and tissue response are identical. Concretions may result from chronic inflammation. Inflammation of this gland in other species is very rare.

Prostatitis is a common and classic disease in the dog. It is often a disease of older dogs in which hyperplastic prostatic changes are present. The inflammatory changes contribute to the enlargement in a significant proportion of the cases, but the disease may occur in younger dogs with normal prostates. The infecting agents are usually urinary pathogens, *Escherichia coli*, *Proteus vulgaris*, streptococci, and staphylococci, which invade via the urethra and prostatic duct. Prostatitis occurs in brucellosis of dogs.

Prostatitis is usually recognized when there are systemic signs of illness from endotoxemia, and about two-thirds of affected dogs have a history of urinary tract signs that include blood and or pus in the urine, urethral discharge, incontinence, or dysuria. Except for dramatic elevations in the numbers of neutrophils in the blood in dogs with prostatic abscesses, hematologic data are mostly equivocal, so that cytologic evaluation and culture of prostatic fluid collected by prostatic massage or ejaculation is necessary to differentiate prostatic diseases in the dog.

Diffuse necrotic and hemorrhagic prostatitis is the most severe form. The whole gland is affected by the necrosuppurative process. Septicemia, endotoxemia, peritonitis, severe pelvic edema and cellulitis, and death can ensue. The gland is often asymmetrically enlarged, hemorrhagic and edematous (Fig. 5-52). It pits on digital pressure and the fluid that drains from the cut surface is either blood and edema fluid, or pus. Prostatitis may become emphysematous in the presence of gas-forming organisms. Less severe lesions are multifocal or regional in extent. Some are more suppurative and centered on the acini or hyperplastic cysts, whereas others have variable interstitial involvement; neutrophils dominate in all lesions (Fig. 5-53A). Localization in and destruction of acini proceeds to abscess formation and these may become confluent, converting the whole gland into a multiloculate abscess cavity, but this is unusual. Severe acute inflammation may resolve and leave only extensive scarring, or it may become chronic, with small walled-off foci.

Chronic prostatitis in the dog is a common lesion (Fig. 5-53B). Because affected dogs are often older, there is variable glandular hyperplasia and cystic hyperplasia. The inflammation is segmental and may spare large portions, or is multifocal and coalescing. The prostatic epithelium varies from hyperplastic columnar cells with prominent eosinophilic globules in the apical cytoplasm of individual acinar cells to atrophic where they are cuboidal or squamous in type, and the apical cytoplasm loses eosinophilic staining. Focal squamous metaplasia occurs, and may be mistaken for prostatic intraepithelial neoplasia. The lumina of the glands contain a variable number of neutrophils and macrophages, and debris. The interstitium has lymphocytes and plasma cells and aggregates of lymphocytes; true lymphoid follicles are common. Fibrosis is variable; often some regions have extensive fibrosis such that the interstitium has a larger area than acini. Dogs with clinical prostatitis are often treated with antibiotics and neutering—the latter results in superimposition of physiologic prostatic atrophy on the effects of fibrosis and chronic cellular reaction.

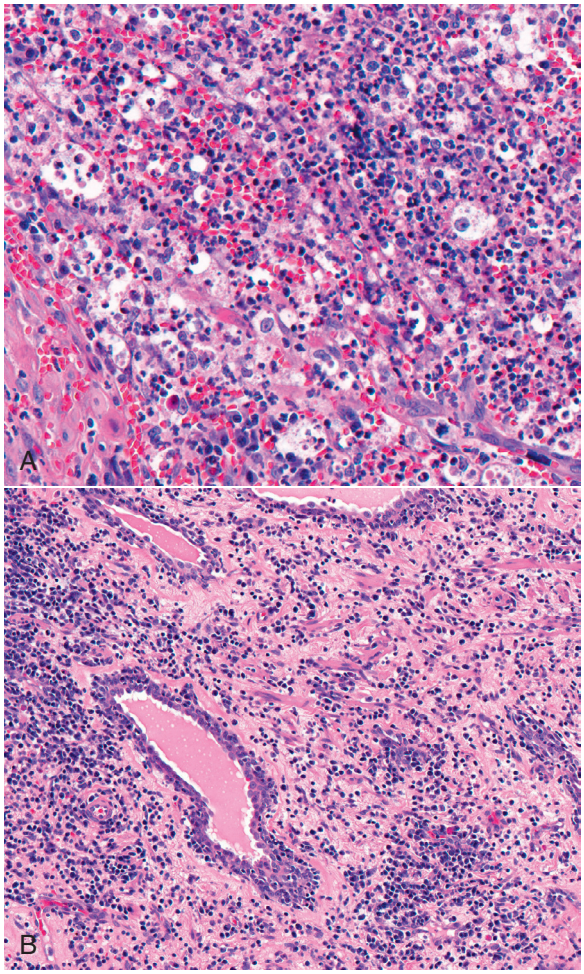

Figure 5-53 **A.** Histologic appearance of **suppurative prostatitis** with destruction of glandular lumina with predominantly neutrophils, lesser numbers of macrophages, and interstitial edema. **B.** Lymphocytic prostatitis with lymphocytes, plasma cells, and abundant fibrous tissue in the interstitium of the prostate of a dog.

Prostatitis is a constant feature of *Brucella canis* infection. Typically, involvement is extensive but lobular in distribution, and consists of many lymphocytes in the interstitium. There is often fibrosis and atrophy or loss of adjacent epithelium.

Apart from bacterial prostatitis, systemic fungal infections caused by *Blastomyces dermatitidis*, *Cryptococcus neoformans*, and *Coccidioides immitis* may involve the prostate. There are reports of prostatitis with *Mycoplasma canis* and *Leishmania* spp. recovered from the lesion or seminal fluid.

Prostatitis in bulls, boars, stallions, rams, bucks, and tomcats is very rare, but when present, has a similar range of changes as occurs in the dog.

Hyperplasia and metaplasia of the prostate and bulbourethral gland

Hyperplasia or metaplasia of the bulbourethral glands is rare. Reversible enlargement of the bulbourethral glands with squamous metaplasia, hyperplasia, and cystic dilation occurs in wethers ingesting strains of *clover with high estrogenic potency*, such as *Trifolium pratense, T. repens, T. subterraneum*. In wethers, but not in rams, grazing potent green clover pastures induces the bulbourethral glands to become large and firm with a marbled cut surface. They may also contain cysts that are large enough to cause fluctuant swelling of the perineal region. These are filled with urine and cellular detritus because they communicate with the urethra via the ducts of the gland. The epithelial hyperplasia may obstruct the urethra. Cystic uterus masculinus develops too, and there may be mammary development (for effect on females, see Vol. 3, Female genital system). Prolapse of the rectum also occurs. The *prostatic changes* are visible as chalky or yellow streaks and flecks on the dorsal surface of the urethra. Microscopically, there is squamous metaplasia with central keratinization.

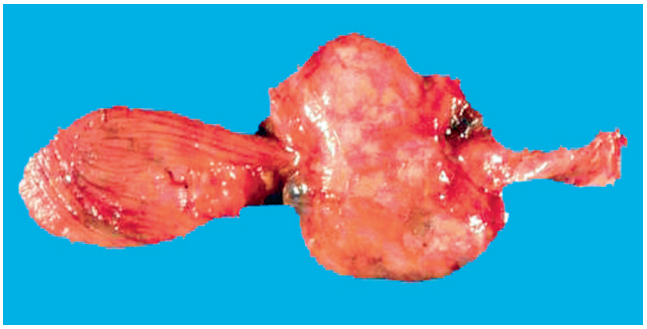

Figure 5-54 **Prostatic hyperplasia** in a dog with almost symmetrical enlargement of the prostate gland.

Marked squamous metaplasia, especially of the vesicular glands, of bulls follows ingestion of *chlorinated naphthalenes*. Nodular hyperplasia of the bulbourethral glands of rams occurs occasionally as an incidental finding.

Prostatic hyperplasia is very common in dogs, and is testosterone dependent (Fig. 5-54). It also occurs in the bull. The entire prostate is larger; nodular hyperplasia is very rare. The prevalence and degree of hyperplasia increases with advancing years, such that 80% or more of mature or old dogs have an enlarged prostate.

Enlargement of the prostate frequently causes *obstipation*. The colon is obstructed when the prostate is forced into the pelvic inlet as the dog assumes the position for defecation and increases abdominal pressure. Less common is *interference with urination*. Urinary retention occurs. It is impossible to demonstrate compression of the urethra, the urethra is not surrounded by the prostate gland, and in the living animal, incontinence is common and urine can be expressed easily. Pressure of the enlarged gland on the sacral parasympathetic nerves may be responsible, as is attenuation of the urethral lumen by longitudinal stretching when the prostatic enlargement is sufficient to cause displacement forward into the abdomen. Acute infections of the urinary tract and hydronephrosis often complicate urinary retention.

A *higher estrogen:testosterone ratio* underlies prostatic hyperplasia in dogs. Prolactin may also be involved. Hyperplasia does not occur in castrated dogs, and castration causes a reduction in size. The exception is extremely rare, that is, when a castrated dog has an estrogen-secreting tumor. At puberty, epithelial hyperplasia is coincidental with normal testicular development and hormone production. Throughout life, the testosterone and dihydrotestosterone concentration in serum is unchanged, but it increases in prostatic secretion with age. Testosterone receptor content in each cell is not changed. The 17β estradiol:testosterone ratio is increased in those dogs with prostatic hyperplasia. Estrogens act synergistically with androgens to potentiate hyperplasia of the epithelium. It is unclear

in spontaneous prostatic hyperplasia, however, whether and to what extent estrogen induces accompanying stromal changes.

The hyperplastic gland is large and the surface is either smooth and regular or irregularly nodular (see Fig. 5-54). Larger prostates have a less obvious bilobed appearance. Fluctuating cysts and venous and lymphatic ectasias may be present beneath the capsule. The appearance of the cut surface depends on the degree of acinar and stromal hyperplasia and on the presence and size of cysts. The lobules vary in size and may be poorly defined, or well defined if there is a prominent increase in amount of the interlobular stroma.

The glandular elements are often sponge-like in appearance because there are numerous small cysts containing milky fluid. The cysts are irregularly distributed, but the largest ones tend to be located beneath the capsule. The prostatic urethra may have small yellow elevations of the mucosa corresponding to the papillae of the excretory ducts. Microscopically there is lobular hyperplasia, stromal hyperplasia and condensation, and cyst formation variously interspersed. The acinar hyperplasia consists of hyperplasia and hypertrophy of the epithelial cells often with papillae, but there is always a single layer of epithelial cells on an intact basement membrane. Within the same lobule, some acini may be cystic, and these are of irregular size, round, and lined by epithelium that is attenuated (Fig. 5-55). There may be secretion in the lumen. The interlobular connective tissue is increased in amount to various degrees and density, and may exist as broad sheets with some extension into the intralobular stroma. In most instances, this interstitial tissue contains some lymphocytes and plasma cells but the epithelium or acinar lumen is not affected.

There is no clear distinction between a normal prostate and one that is in the early stages of hyperplasia, although arbitrary decisions are based on the weight or size of the gland relative to body weight and for a specific age. The relative weight corrected for age is fairly consistent, except in Scottish Terriers in which the relative weight of the prostate is about 4 times that of any other breed. Although estrogen is therapeutically effective in causing temporary regression of an enlarged prostate, rapid enlargement of the gland follows.

Squamous metaplasia of the epithelium may occur in dogs with Sertoli cell tumors, or following the administration of *estrogens*. The metaplastic change may involve acini in all parts of the gland as well as the prostatic urethra, uterus masculinus, and ducts. Affected epithelium becomes stratified squamous in type, with keratin squames in the lumen. Neutrophils and macrophages are often in the lumina too. There is no evidence that squamous metaplasia of the canine prostate is a preneoplastic change.

Squamous metaplasia occurs in swine exposed to estrogenic mycotoxins such as zearalenone. In cats, prostatic enlargement with epithelial hyperplasia and cystic dilation of glands follows estrogen administration. Metaplastic cornification is restricted to urethral epithelium.

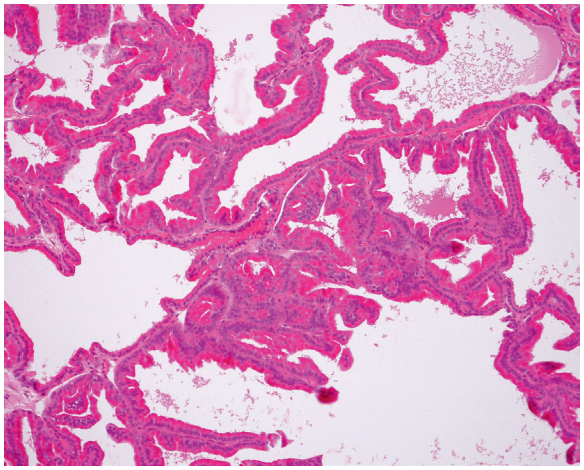

Figure 5-55 Microscopic appearance of **prostatic hyperplasia**. The acinar epithelial cells are tall columnar with prominent eosinophilic granules in their apical cytoplasm, and the acini are cystic.

Neoplasms of the prostate and bulbourethral gland

Neoplasia of the accessory genital glands is rare in all domestic mammals, although **carcinoma of the prostate in dogs** is a well-known and intensely studied disease used in comparison with human prostatic carcinoma. The original site of development and the classification of carcinomas is debated and opinions vary. Neoplasms may arise from the pelvic urethra, prostatic ducts, or glandular acini, and the phenotypes vary from adenocarcinoma to transitional cell carcinoma to squamous cell carcinoma and mixtures of several types. The majority are poorly differentiated and a mixture of types. Because dogs castrated prior to puberty develop carcinoma with equal frequency to nonneutered males, a urothelial phenotype is often suggested, given that about half of cases will express urothelial phenotypic markers (such as uroplakin). Immunohistochemical and proteomic studies have failed to adequately classify these tumors accurately or to show a prognostic difference.

The prostate and urethra arises embryologically from endodermal epithelium, so separation of the different types is fundamentally difficult. Studies so far have failed to conclusively indicate a prognostic difference between the types. It is better to group the neoplasms as carcinoma of the prostate, and to avoid classification without ironclad outcome-based data.

The cause of prostatic carcinoma is unknown. The prevalence of hyperplasia of the prostate and the rarity of neoplasia suggest they are not linked. Low-grade prostatic intraepithelial neoplasia (PIN), as occurs in human males, does not occur as a solitary lesion in dogs except in very rare situations. Even then, separation of PIN from squamous metaplasia or other change in prostatitis is difficult. High-grade PIN does occur in prostates with carcinoma.

The high relative prevalence in previously neutered dogs suggests that hormonal influences are not involved, at least not in those animals. Prostatic neoplasia is not causally related to testicular neoplasia.

Prostatic carcinoma occurs mostly in old dogs, especially those older than 10 years. Clinical signs mimic those of prostatic disease generally, and fall into 2 main categories. Many dogs develop dysuria, stranguria, and obstruction. Some have fecal obstipation, whereas others have emaciation and hindlimb locomotory disturbances, apparently a result of metastasis to the lower lumbar vertebrae, bones of the pelvis, and long bones of the rear limbs. Spread of neoplastic cells to bone is via the vertebral venous plexus, systemic circulation, or direct extension.

Enlargement of the prostate with carcinoma is more likely to be asymmetric and irregular than in hyperplasia (Figs. 5-56, 5-57). A severe fibrosing reaction with neoplastic cells may

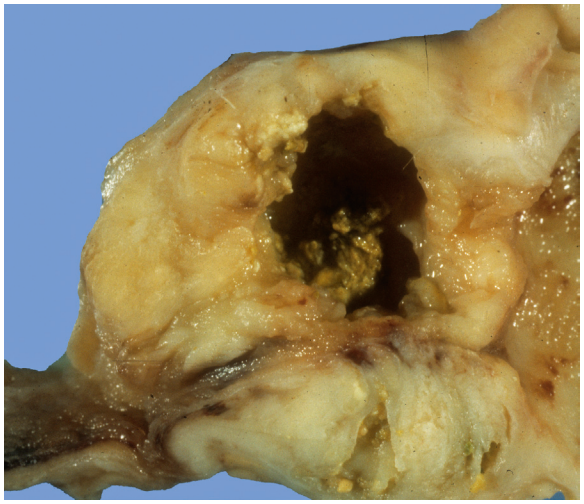

Figure 5-56 Carcinoma of the prostate in an older dog castrated before puberty. The phenotype is transitional cell carcinoma that had a small primary with a central cavity of necrosis. This neoplasm was widely metastatic.

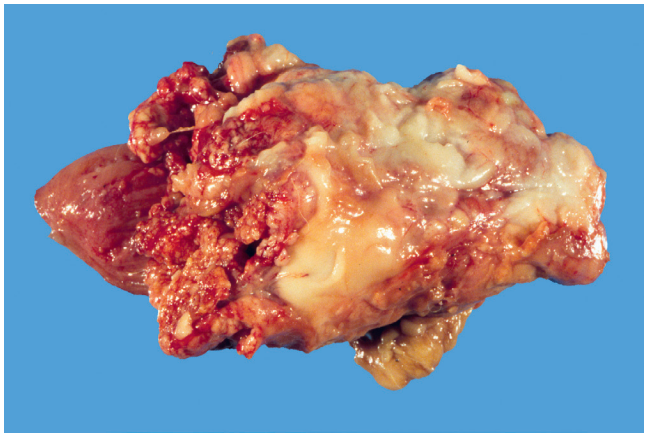

Figure 5-57 Carcinoma of the prostate in a dog. Extensive invasion of the neoplasm into the surrounding tissues with filling of the pelvis is evident. No distant metastases were found.

occur, and such neoplasms are hard and tough and sometimes contain foci of bone. The capsule of the prostate and adjacent organs often is invaded and becomes adherent to the pelvis (see Fig. 5-57). Cyst formation is common. Neoplastic tissue may extend into the sublumbar area. Metastasis is to iliac and pelvic lymph nodes, bone, kidneys, bladder, lungs, liver, heart, mesentery, and omentum. Neoplastic cells may also be observed in the urine and occasionally in blood smears. Hypertrophic osteopathy can result.

Microscopically, heterogeneity and poor differentiation is a feature of carcinoma of the prostate. Pleomorphism, anisokaryosis, and a high mitotic index are usual. A high proportion of carcinomas have a mixed phenotype with glandular and ductular components, and transitional cell morphology (Fig. 5-58). Attempts to subdivide carcinomas into different types is subjective, and there is a lack of consistency and rigor. Spindle cell carcinoma is very rare.

Other, rare, neoplasms of the canine prostate include adenoma, soft tissue sarcoma, hemangiosarcoma, leiomyosarcoma, and osteosarcoma.

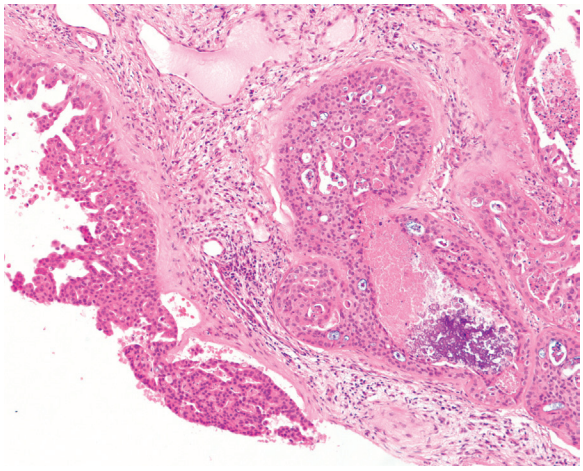

Figure 5-58 Carcinoma of the prostate in a dog. The carcinoma has variable phenotypes with both transitional cell and glandular differentiation.

Carcinoma of the prostate occurs in the **cat**. The prostate is separate from and at a distance caudal to the bladder and it covers the urethra dorsally and laterally. As in the dog there is usually a history of dysuria and hematuria. Affected prostates measure up to 2 cm or greater, are white to cream, and microscopically have acinar or ribbon arrangement of pleomorphic epithelial cells. Mitoses are frequent. Pulmonary metastases may occur.

Secondary tumors, especially lymphoma, are found with disseminated disease, although the prostate is not routinely examined by many. Transitional cell carcinomas of the neck of the bladder may invade the prostate.

Neoplasia of the bulbourethral gland is exceptionally rare. Hemangiosarcoma was found in the bulbourethral gland of the goat.

Miscellaneous conditions of accessory genital glands

Atrophy of the accessory genital glands occurs following castration, in advanced age, and sometimes with chronic inflammation. The glands become small, dense, and of tough consistency. Atrophy of the vesicular glands and ampullae accompany epididymal or deferent duct obstruction of the ipsilateral side.

In the dog, rapid atrophy occurs after adult castration. The degree of atrophy is dependent on its size at castration—many become one-fourth the normal size. Microscopically, acinar and ductal epithelial cells decrease in size, become less differentiated and more basophilic until epithelium is flat, and after 3 months the acinar lumina are small or nonexistent. The stroma becomes more conspicuous, and smooth muscle of the capsule and trabeculae disappears and is replaced by dense fibrous tissue. Ultrastructurally, within 3 days the epithelial cells were small and contained large lipid droplets.

Corpora amylacea occur in the accessory genital glands of domestic animals. *Concretions* in the vesicular glands, bulbourethral glands, or prostate develop from retained secretions or in cases of chronic inflammation. In bulls, vesicular gland concretions are up to 1.5 cm or more in diameter, irregular, friable, rough externally, and distinctly laminated on section. They are usually found in inflamed vesicular glands and the

lining of the concretion cavity varies from normal to pseudostratified. Their structure is amorphous eosinophilic debris with occasional clumps of enmeshed nuclear material. Concretions are composed of organic components, phosphates, carbonates, and spermatozoa—so-called "*semen stones*." Microconcretions are common in the vesicular glands of rams, unassociated with inflammation.

In dogs, the occurrence of prostatic concretions or calculi is extremely rare and such calculi may be confused with urinary calculi. One report of a 30 × 20 × 10 mm laminated prostatic calculus composed of calcium carbonate and struvite suggested that it resulted from reflux of urine. Calculi are normally 1-5 mm in diameter, hard, white, and spherical, and consist of phosphates and carbonates of calcium as well as urates and oxalates. These form around a crystallization point of organic material—mostly desquamated gland epithelium. Calculi seldom elicit clinical signs. Prostatic calculi are reported in sheep.

Metaplastic ossification of prostatic stroma occurs in the dog, usually with neoplasia. Foci of mineralized bone could be mistaken for calculi on radiographic examination.

Intraductal foreign (plant) material and chronic adenitis affected the bulbourethral gland of a bull.

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PENIS AND PREPUCE

The penis and prepuce develop from the urogenital tubercle. The preputial cavity only forms when the epithelial recess separates just before puberty. The penis attaches to the ischium and ends with the head of the penis. In all species except the dog, the intrapreputial component of the penis includes the head and a short part of the body of the penis. The head of the penis is longest in the dog, where it includes the erectile bulbs of the penis and is the only intrapreputial part. The penile urethra forms ventrally. Small ruminants have a urethral process, and in the cat, the *penile spines* or barbs are testosterone dependent. The stallion has a sebaceous secretion in its prepuce that is *smegma*. In the other species, the internal prepuce is a mucous membrane.

Disorders of development of the penis are many, and are part of the myriad disorders of sexual development (DSD). Some are surgically correctable, others are functional abnormalities, and others prevent intromission and or do not allow fertilization. The number and complexity of the disorders of development is great, so only the more common and or important are listed here.

Penile and preputial hypoplasia results from a lack of testosterone at critical time periods—from development of the penis to puberty. This occurs in early castration and in many DSD. Bulls have a form of hypoplasia described *as congenital short penis*, possibly associated with shortening of the retractor penis muscle. Penile protrusion (penile tip to preputial orifice) is 10-22 cm as opposed to 25-42 cm in normal matched controls. Partial or complete *lack of the sigmoid flexure* of the penis occurs in bulls and rams. Hypoplasia of the head of the penis only is reported. Other rare disorders of sexual development in the bull include abnormal insertion of the retractor penis muscle, with stretching of the skin cranial to the testis during erection, partial or complete duplication of the penis, supernumerary ectopic penis, and detached urethral process in which the free end of the penis has a bifid appearance resembling diphallia. *Diphallia* is reported in several species, including the bull, ram, and tomcat.

Defects of the urogenital system may have a penile urethral component. Congenital dilation of the penile urethra is described in the goat.

Directional deviations of the erect penis occur with persistence of balanopreputial folds—regions in which the prepuce failed to separate from the penile epithelium. A well-known fold is the *persistent penile frenulum*, which occurs when the penile frenulum fails to separate from the prepuce. Persistent penile frenulum is reported in the bull, boar, buck, dog, and tomcat. Although studies in the boar have indicated some breed susceptibility for persistent frenulum, there is no definite evidence for inheritance of this trait in any domestic species. *Deviation of the penis* occurs with asymmetrical development of the cavernosum of the penis in the horse and donkey, malfunction of the apical ligament in the bull and ram, and congenital curvature of the os penis in the dog.

Erectile dysfunction, failure of erection of the penis, is rare. Erection requires central nervous system control, local nervous control with contraction of the ischiocavernosus muscles, and vasoconstriction of veins. This allows arterial input to the erectile tissue of the cavernosum and spongiosum but occludes venous drainage. Vascular defects of the penis that cause failure of erection are studied in the bull and boar, but their precise diagnosis antemortem or postmortem requires injection of contrast material and radiography, or injection of plastic into vessels to form casts. *Vascular shunts* from the cavernosum to the spongiosum of the penis or to peripenile vasculature prevent effective erection. Congenital shunts from the cavernosum to neighboring veins in boars can be inherited. Immunohistochemical studies of impotence in the boar provided evidence that defective innervation contributes, with depletion of vasointestinal polypeptide (VIP) reactivity in penile nerves.

Penetrating injuries and traumatic fistulas of the erectile tissue and the urethra or external tissues leads to hemorrhage that can be life threatening. This, in the bull, includes forced deviation and rupture of the penis with subsequent hematoma formation. Penile hematoma resulting from forced deviation of the penis occurs in bulls and rams at the distal bend of the sigmoid flexure, but sometimes proximal to it (Fig. 5-59). In stallions, rupture of the cavernosum outside an intact tunic (tunica albuginea) of the penis is more frequent; trauma is the likely cause. Other vascular lesions include varicosities of

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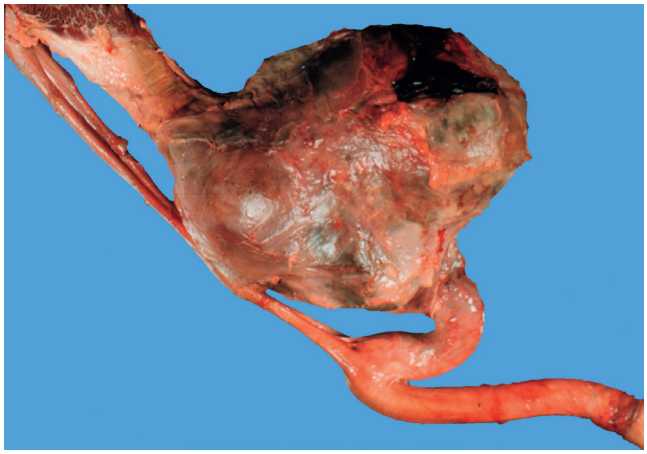

Figure 5-59 Forced deviation of the penis resulted in **rupture of penile tunic and hematoma** proximal to the sigmoid flexure in a bull.

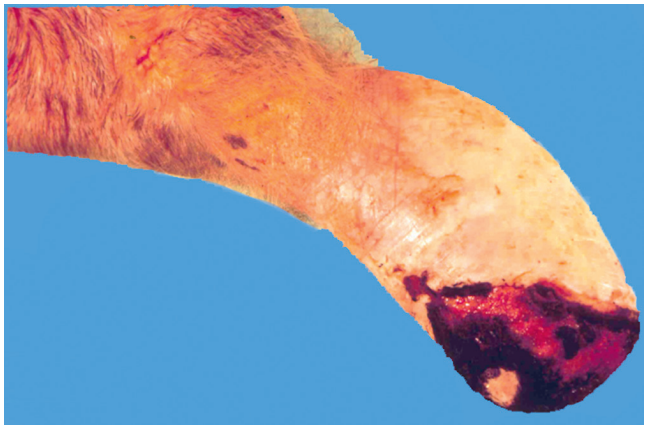

Figure 5-60 Preputial eversion and prolapse in a bull. The prepuce cannot be retracted and is ulcerated and hemorrhagic.

preputial veins in stallions that may lead to thrombosis, edema, and inflammation. In dogs, trauma to the cavernosum or root of the penis may occur during attempted copulation and results in hindquarter pain and/or lameness, dysuria, and perineal edema but no obvious hematomas. Extensive thrombosis of the corpus cavernosum penis occurs in stallions, dogs, and cats with priapism, and it was unclear whether the thrombi were the cause or result of pain and persistent erection. In separate stallions, concurrent nematodiasis and metastatic melanoma were considered the primary cause.

Eversion of the preputial mucosa as a temporary event is common in bulls. *Bos indicus* bulls develop prolonged eversion because many have inadequate muscles in the prepuce. Trauma to the everted epithelium and desiccation lead to edema and inflammation (Fig. 5-60).

A *preputial diverticulum* is anatomically normal in the boar but abnormal in other species, such as the bull and water buffalo. Deflection of the penis into the diverticulum by boars results in accumulation of debris, urine, and semen that predispose to local infection and inflammation.

Tearing of preputial mucosa, typically at the ventral preputial fornix, is a common injury that occurs in bulls used for artificial insemination. The precise cause is unknown.

Priapism is prolonged or persistent erection of the penis. More specific definitions include an erection lasting longer than 4 hours without sexual stimulation, or continuous, usually nonsexual erection of the penis, especially caused by disease. Prolonged erect penises become traumatized, dry, or undergo necrosis. Little is reported about the pathogenesis in dogs. In humans, there is a nonischemic form caused by increased arterial flow, and an ischemic form with reduced venous outflow. Dilation and thrombosis of the cavernous sinuses of the penis are found histologically, but it is unknown whether this is a cause or result of priapism. Thrombi are often laminated, suggesting progressive enlargement. A secondary paraphimosis occurs and there will be necrosis of the mucosa, bacterial infection of the eroded surface, and even total penile necrosis.

Paraphimosis, or inability to retract the penis, is a particular problem in the stallion. Trauma is the most common cause, but inflammation from other causes, neoplasia, or primary penile paralysis may be involved. Penile paralysis occurs in severely debilitated stallions, after administration of phenothiazine tranquilizers, or from local neurologic disorders.

In the dog, *fracture of the os penis* leads to obstruction of the urethra. Mineralization and ossification of the penis caudal to the os penis is a frequent (usually radiographic) finding and its prevalence increases with age. Urethral obstruction with hydronephrosis and bladder rupture resulting from aberrant localization of *Ancylostoma caninum* in the caudal os penis is described.

Inflammation of the penis and prepuce (phaloposthitis)

Inflammation of the head of the penis (*balanitis*) is frequently accompanied by inflammation of the prepuce (*posthitis*). Many organisms reside in the preputial cavity, and there is innate and acquired local immunity. Viruses such as bovine parainfluenza virus 3 in bulls and herpesviruses in many species, nonpathogenic and potentially pathogenic bacteria such as *Corynebacterium renale* and *Histophilus somni*, fungi, mycoplasmas and ureaplasmas, chlamydias, and protozoa are isolated from preputial cavities that are normal or have lesions. Ascribing pathogenicity to organisms is therefore difficult, and reports on whether these organisms cause lesions in the prepuce are conflicting and often do not withstand scientific scrutiny.

Lymphocytes, plasma cells, and even lymphoid follicles are commonly found in normal preputial mucosa. They indicate an acquired immune response but the initiating antigens are unknown. Immunoglobulins are present in preputial washings. They are derived from plasma cells of the prepuce or the accessory genital glands. In the bull, the number of plasma cells tends to increase with age. Small (T) lymphocytes, frequently seen in preputial and penile epithelium, participate in cell-mediated immune reactions. The epithelium of the penis and prepuce is of the squamous or transitional type, thus active transport of secretory IgA is unlikely. Innate immunity, with a limited exposure to the external environment, epithelial barrier, and antimicrobial molecules, is very important.

Bovine herpesvirus 1 causes phaloposthitis (commonly called *balanoposthitis*) in the bull. This virus causes both respiratory disease (infectious bovine rhinotracheitis, IBR) and genital disease (infectious pustular vulvovaginitis, IPV). The clinical disease in the bull results in a thin purulent preputial discharge. Simultaneous occurrence of the respiratory and genital forms of the disease is rare. Within 2-3 days of exposure, there are numerous up to 3-mm gray-white opaque foci

of necrosis on the penis. These may form confluent and flat efflorescences. In severe cases, edema of the penis and prepuce may occur. The foci of necrotic mucosa exist for 1-2 days only, then the surface sloughs and sharp erosions remain, especially in the area of the head of the penis. Many erosions are surrounded by a red zone of hyperemia. In uncomplicated cases, healing is complete in 2 weeks. As with any infection of the prepuce, lymphoid follicles develop and are pale to dark red 1-2 mm nodules that raise the mucosal surface.

The microscopic lesions are foci of dead cells within the epithelium and spongiosis. Intranuclear inclusion bodies may appear in epithelial cells. Dead cells slough and shallow ulcers form. Neutrophils migrate into the affected epithelium and lymphocytes appear in the submucosa. As with other herpesviral infections, latency occurs and viral production is reactivated naturally or following treatment with corticosteroids. Although orchitis is reported in bulls, it is exceptional.

The pathogenesis of **equine coital exanthema,** caused by equid herpesvirus 3, are comparable to BoHV-1 in cattle, although the penile and preputial lesions and subsequent erosions are larger, being up to 15 mm in diameter. Lesions in the stallion tend to involve the body of the penis more frequently than the head. They first appear 2-5 days post exposure as vesicles, but rapidly progress to circumscribed yellow pustules with raised borders and depressed centers. Resolution usually occurs within a few weeks, leaving depigmented spots.

Herpesviral infection of male goats (CapHV-1) causes similar lesions that can progress to extensive suppurative and necrotizing phaloposthitis involving the head of the penis, fornix, and entire urethral process.

In dogs, the genital lesions of **canid herpesvirus 1** infection consist of hyperemia, petechial hemorrhages, and the development of lymphoid nodules, especially over the base of the penis and the preputial reflection. There is a serous discharge from the preputial orifice. Lesions appear about 3 days after experimental infection, but are self-limiting, and regress 4-5 days subsequently, with no apparent sequelae. Simultaneous conjunctivitis may occur. Recurrence of lesions, an important feature of the disease in bitches, seems to be less common in the male. Pustule formation and ulceration do not appear to be a feature of genital herpesvirus infection in the male dog even though virus can be isolated from the penis of infected dogs following immunosuppression with prednisolone.

A mild *balanoposthitis*, not associated with herpesvirus infection and presumed to be bacterial in origin, is common in dogs. Depending on duration, there is intense hyperemia of the epithelium, erosion, and mucopurulent exudate. Lymphoid follicles become enlarged and prominent. Hemolytic strains of *Escherichia coli* are most frequently isolated from such cases, other common isolates being *Proteus vulgaris* and hemolytic streptococci.

Multiple pale dome-shaped papules up to ~3 mm in diameter on hairless parts of the equine prepuce, and on the muzzle, may result from infection with the molluscum contagiosum virus (Molluscipoxvirus) (for details see Vol. 1, Integumentary system). Histologically, discrete epithelial hypertrophy and hyperplasia with characteristic "molluscum bodies" are present.

Outbreaks of **ulcerative posthitis in bulls** occur occasionally, but these are less severe than in sheep (see later). The cause and pathogenesis of this condition is unknown. *Corynebacterium renale*, an inhabitant of the prepuce of apparently healthy bulls, is frequently isolated from bulls with ulcerative posthitis, and as animals on a high plane of nutrition are predisposed, a parallel of this condition with ovine posthitis is suggested. However, it is not clear why steers are infrequently affected. Mild to severe erosions and ulceration with edema are confined to the preputial orifice and cranioventral area of the prepuce. Lesions begin as small raised areas of necrosis that leave shallow erosions. The ulcers are irregular in shape, may be several centimeters in diameter, are sharply defined and frequently bleed. The histologic appearance of lesions is nonspecific, with superficial necrosis, reactive epithelial hyperplasia, and underlying granulation tissue. Causal organisms cannot be demonstrated histologically in the lesions that precede ulceration. In more severe forms there is increasing edema, abscessation, and even myiasis. Deformity of the preputial orifice and phimosis may occur following healing of ulcers.

Traumatic injury with subsequent infection by such organisms as *Trueperella pyogenes, Escherichia coli*, streptococci, and staphylococci is common in bulls. Less common lesions include balanoposthitis from infection with the larvae of *Strongyloides papillosus.* Tuberculous balanoposthitis, with characteristic granulomas involving the penis or prepuce, is seen occasionally in bulls from infected herds, sometimes as the only lesion. Genital transmission is possible. The presence of *Campylobacter fetus* subsp. *venerealis* in the preputial sac does not produce gross or histologic changes. Likewise, specific lesions do not accompany preputial infection in bulls by *Tritrichomonas foetus.* Microscopic examination of infected penile and preputial epithelium may reveal cells and debris in crypts, and a typical lymphocytic submucosal reaction. Rarely can trichomonads be demonstrated in histologic sections. Recognition of the carrier state in bulls in the absence of lesions in both campylobacteriosis and trichomoniasis emphasizes the need for diagnosis by culture or molecular techniques.

Preputial diverticulitis occurs in swine, and the characteristic plaques and ulcers occur in the preputial diverticula of 25-40% or more of castrated and entire male pigs. The lesions begin as foci of hyperkeratosis and progress to distinct white-gray plaques 2-4 mm in diameter with obvious para- and dyskeratosis. Yellow-brown ulcers up to ~10 mm in diameter with raised borders form (Fig. 5-61) following central necrosis, sloughing of epithelium, and infiltrating neutrophils. Such lesions may become confluent, and hemorrhage from them is common. Calculi may be present in the diverticulum. The precise cause of preputial diverticulitis in pigs is unclear, but

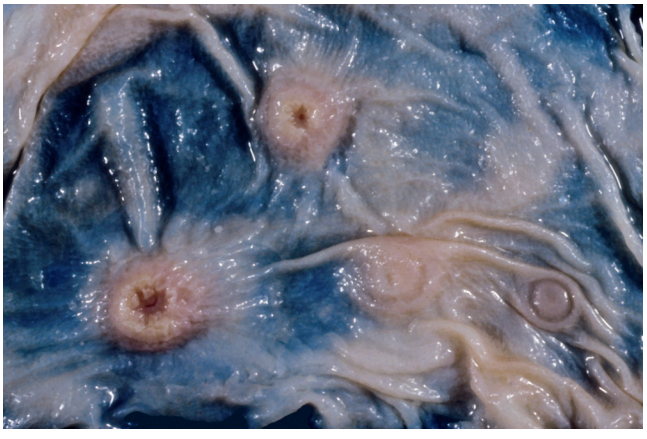

Figure 5-61 **Ulcers** of the preputial diverticulum of a boar.

accumulation and decomposition of urine is important. *Actinobaculum suis*, a cause of pyelonephritis and cystitis in sows, may be isolated from the prepuce of boars with diverticulitis and healthy boars alike; the likelihood of venereal transfer exists. Other bacteria frequently present in the diverticulum include *Proteus* spp. and staphylococci. There is no correlation between types of bacteria present and boar performance. Older pigs are more likely to develop ulcers. An age-related change in the bacterial flora of the diverticulum occurs, *Actinobaculum suis* being generally more common in pigs >4 months of age and in adult boars than in younger animals. Spirochetes also colonize the preputial diverticulum and may contribute to inflammation.

Marked and apparently selective infestation of muscles of the penile urethra in **pigs** may occur several months after infection with *Sarcocystis miescheriana* from dogs. Microscopically, there is degeneration of muscle fibers; eosinophils with fewer lymphocytes and macrophages are present.

Balanoposthitis is an uncommon lesion in the **stallion** but occurs in dourine, caused by *Trypanosoma equiperdum* (see also Vol. 3, Female genital system). Primary infection in **dourine** occurs in the genitalia, following transmission by coitus. There is marked edema of the prepuce and adjacent areas, and phimosis may result. In many cases, yellow-red nodules up to ~8 mm in diameter may subsequently appear on the penis especially near the urethral orifice. These later transform to shallow ulcers, which after healing may leave distinct nonpigmented foci on the skin of the penis, prepuce, scrotum, and perineum. In **cutaneous habronemiasis** (for detailed discussion, see Vol. 1, Integumentary system) the lesions may affect the penis, especially around the urethral meatus, and or the preputial mucosa at about the point of its contact with the end of the retracted penis. The lesions are elevated, ulcerated, and bleed; they consist of exuberant fibrous tissue enclosing few or many larvae of *Habronema* spp. and may be sufficiently large to cause paraphimosis. There are large numbers of eosinophils that form small eosinophilic "abscesses" around immobilized and dead larvae; they correlate to small yellow foci on the cut surface. The lesion develops during the summer months. *These larvae often infect squamous cell carcinomas*, so lesions should be examined for neoplasia. Nodules in the prepuce of the stallion are also caused by adults, larvae, and ova of *Halicephalobus* spp., or by mycotic infection, particularly pythiosis. *Geldings* develop a nonspecific posthitis with accumulation of smegma and detritus, presumably because of reduced penile extrusion.

In sheep, **ulcerative posthitis of wethers,** and occasionally of rams, is common and important. Vulvitis may occur in ewes in affected flocks. Wethers are particularly susceptible, suggesting incomplete development of the prepuce and penis, and/or the tendency of wethers to urinate within their sheath.

Development of the primary lesion depends on the occurrence of a transmissible, urea-hydrolyzing bacterium such as *Corynebacterium renale*, and on the excretion of urine rich in urea. In one outbreak, *Rhodococcus equi* and *Corynebacterium hofmanni*, both of which produce urease, were isolated from lesions. Other factors in urine, possibly hormonal in origin, may also be involved. High protein and especially leguminous diets predispose to the disease and the incidence is lowest during the summer. It is presumed that wethers are infected by the transmission of material on contaminated bedding, herbage, or by flies. Venereal transmission from rams to ewes also occurs.

The lesion in wethers begins as a small yellow area of epithelial necrosis at the orifice of the prepuce, often dorsally. This ulcerates and there is slow expansion of the lesion and granulation that results in stenosis and occlusion of the preputial orifice. Secondary lesions occur when the prepuce becomes swollen from the accumulation of urine or pus. Extensive internal ulceration of the prepuce develops, the urethral process is destroyed, and the head of the penis ulcerates. The common name applied is *pizzle rot*.

A severe **ulcerative balanitis,** distinct from the aforementioned condition, occurs in border Leicester rams and in Dorper sheep. Ewes mated to them develop vulvovaginitis. Outbreaks occur in a flock. Deep ulcers up to several centimeters in diameter occur on the ventral surface of the penis. Excessive granulation tissue and variable hemorrhage follows. Necrotic and purulent material covers the head of the penis and urethral process. Adhesions of the penis and prepuce result. Ewes in contact with affected rams have shallow ulcers on the ventral commissure of the labia and posterior vagina. The causative agent(s) is not known, and it is not clear why these rams are predisposed.

Traumatic injury by the cocklebur (*Xanthium strumarium*) may cause outbreaks of severe "acroposthitis" in rams with subsequent suppurative vaginitis in ewes mated to them.

Proliferative lesions of the penis and prepuce occur in dogs with **leishmaniasis,** and misdiagnosed as transmissible venereal tumor. The lesions, which develop over a period of several months, are multiple ulcerated nodules up to ~1 cm in diameter located on the penile tip and preputial mucosa, as well as other organs. Histologically, macrophages containing amastigotes of *Leishmania infantum* dominate the lesions.

Miscellaneous conditions causing variable inflammation of the penis and prepuce include *intrapreputial foreign bodies* such as sand, and "*hair ring*" in the bull, ram, buck, and cat, in which hairs encircle and may constrict the penis.

Neoplasms of the penis and prepuce

The important primary tumors are fibropapilloma in the bull, squamous papilloma and squamous cell carcinoma in the horse, and papillomas and transmissible venereal tumor of dogs. Additional details on bovine fibropapillomas and canine transmissible venereal tumor are in Vol. 3, Female genital system.

Fibropapillomas in bulls caused by bovine papillomavirus 1 occur on the head of the penis. They are most common in young bulls, 1-2 years of age, and are noticed after mating, when hemorrhage occurs. They are usually multiple and up to several centimeters in diameter (Fig. 5-62). Tumors are pink or gray-white on section and are composed mainly of fibrous tissue with an epithelial covering (Fig. 5-63). Histologically, there are differences between tumors in young and old bulls, those in young bulls being more cellular with frequent mitoses.

Although benign, large fibropapillomas in bulls interfere with free movement of the penis through the preputial orifice and prevent retraction of the head of the penis. In such cases, preputial hairs may surround the prolapsed penis and cause strangulation. Alternatively, continued growth of the mass within the preputial cavity may prevent penile protrusion. The urethra can become obstructed and rupture, causing extensive cellulitis.

A *transmissible genital papilloma* occurs in swine and the virus is likely a *Sus scrofa* papillomavirus**.** Both the natural and experimental papillomas regress with time. The tumors are

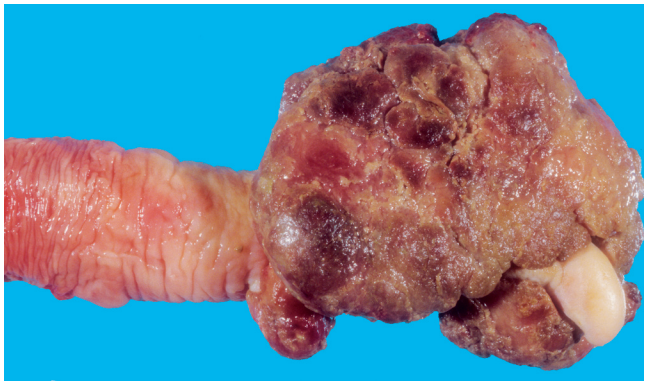

Figure 5-62 Transmissible fibropapilloma in a bull. The exophytic growth may be mistaken for squamous cell carcinoma.

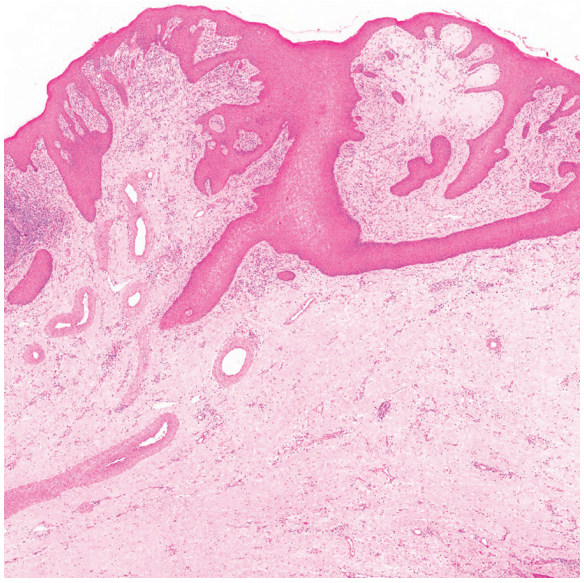

Figure 5-63 Histologic details of **transmissible fibropapilloma** in a bull. The stroma is fibrous tissue and the epithelium has long projections that extend into the stroma.

small, round, and project 3 mm from the mucosal surface of the penis or within the preputial diverticulum. Histologically, they have marked thickening of the epithelium. There is little proliferation of the underlying connective tissue. A thin layer of keratinizing cells covers the hyperplastic epithelium.

Squamous papilloma in all species is a benign, keratinizing epithelial papilliform tumor with little fibrous stroma; it is usually small. Squamous papilloma is most common in the *horse* and *dog*. They can progress to squamous cell carcinoma. Although not all have identifiable virus, many probably are the result of papillomavirus infection.

Squamous cell carcinoma (SCC) of the penis and prepuce is described in the horse most commonly, and also in the dog and bull. It is possible the bovine cases were misdiagnosed fibropapillomas. In the horse, SCCs occur with about equal frequency in stallions and geldings and the average age is >12 years. Because SCC in the equine penis and prepuce occur at sites of prior removal of squamous papilloma, any papilloma in these locations should be considered as premalignant. *Equus caballus* papillomavirus 2 is implicated in the formation of SCC. Over-expression of p53 is also involved. Tumors arise mostly from the head of the penis, and the desmoplastic

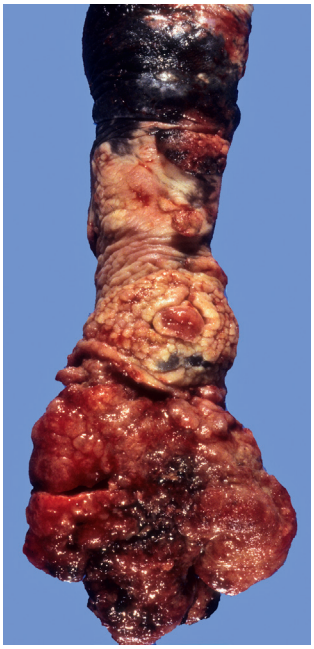

Figure 5-64 Squamous cell carcinoma of the penis of a horse. Squamous cell carcinomas cause enlargement of the penis; some form an exophytic mass (seen here), others form a large tough penis from the desmoplastic response to the neoplastic cells.

reaction is such that many cause the head of the penis to be larger, and firm and tough. Superficial ulceration and necrosis of large tumors are common (Fig. 5-64). Histologically, the penile tumor is well differentiated and keratinization is usually present. Eosinophils are common around the tumor, and foci of necrosis and mineralization are frequent. The tumor invades the corpus cavernosum and metastasizes, especially to the inguinal lymph nodes and less frequently to other organs such as lung or liver.

In the **dog,** SCC of the penis and prepuce is thought to be papillomavirus related. Its appearance is similar to equine SCC but may be nonkeratinizing. Approximately 25% of reported cases had metastasized, chiefly to the inguinal lymph nodes.

Canine transmissible venereal tumour (CTVT) in the male dog arises on the penis or within the prepuce. They may be single or multiple, sessile or pedunculated, nodular or papillary, soft to firm consistency, and up to ~15 cm in diameter (Fig. 5-65). Histologically, they are solid sheets of uniform round, ovoid, or polyhedral cells with large round vesicular nuclei. The vacuolation of the cytoplasm at the cell membrane, a characteristic finding cytologically, is sometimes seen histologically. The mitotic index is high. Metastasis occurs in up to 5% of cases and may involve the superficial inguinal lymph nodes, skin, and multiple other organs. Most cutaneous metastases are probably from trauma and mechanical implantation. Spontaneous regression of some tumors occurs, and most are sensitive to chemotherapy with vincristine.

CTVT is the first naturally occurring neoplasm that is spread by the transferring of cells from an affected dog to another, thus is an allograft. It is venereally transmitted. The cells of CTVT have a chromosomal number of 57, 58, or 59. The dog has 78. Chromosomal and molecular techniques show that neoplasms from different continents and collected decades apart are clonal, and, although there are 2 subtypes,

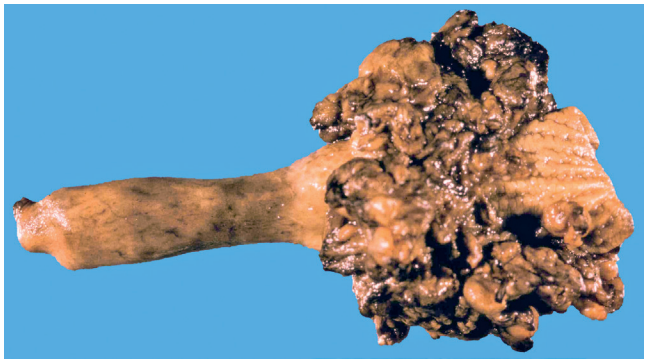

Figure 5-65 Canine transmissible venereal tumor on the penis of a dog.

they have a common origin. The DNA of the CTVT has closely related DNA of wolves and East Asian dog breeds.

The cells of a CTVT avoid detection by immune cells. They downregulate MHC I molecules and there is no MHC II activity, because they secrete inhibitory cytokines (TGFβ1 and IL 6). In the initial proliferative phase of CTVT, they express little MHC class 1 or 2. After about 12 weeks in an experimental model, MHC expression increased dramatically and lymphocytes appear; at the same time, the masses stopped growing. It appeared that the lymphocytes stimulated MHC expression and are responsible for regression of the tumors.

The phenotype of the cells was the subject of considerable debate. Immunohistochemical staining characteristics suggest they are of histiocytic origin, as they are positive when stained with vimentin, often positive with α1-antitrypsin and lysozyme, and negative for CD3, immunoglobulins, and cytokeratin (for more detail, see Vol. 3, Female genital system).

Less common tumors of the penis or prepuce in dogs include the epithelial, mesenchymal, round cell and other tumors (such as melanoma) found in other parts of the body. Of the epithelial tumors, apocrine sweat gland adenocarcinoma is reported. Mesenchymal tumors include lipoma, hemangioma, hemangiosarcoma, soft tissue sarcoma, mesenchymoma, and osteosarcoma, chondrosarcoma, and ossifying fibroma of the os penis of the dog. Sarcoids are found in the penis and prepuce of the horse. Round cell tumors include lymphoma, mast cell tumor, and plasmacytoma. Malignant melanoma is reported in several species.

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For more information, please visit the companion site: PathologyofDomesticAnimals.com

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